MEDICAL LIBRARY

DEC 18 1933

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL. 7 (O. S., Vol. XII) DECEMBER, 1933 NUMBER 6

CONTENTS

	Page
The Pathologic Anatomy of the Liver in Exophthalmic Goiter. Donald C. Beaver and John DeJ. Pemberton	687
Bromide Psychoses: Diagnosis, Treatment and Prevention. Max Levin	709
Subacute Bacterial Endocarditis. John H. Musser	715
The Rôle of Desensitization in Recovery from Bacterial Infection. W. B. Wherry	728
The Familial Incidence of Peptic Ulcer. Herman H. Riecker	732
Toxicology and Assay of Methylene Blue. David I. Macht and Wilton C. Harden	738
Conservatism, the Keynote in the Treatment of Tuberculosis. C. H. Cocke	746
The Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion; and a Comparison with the Effects of Histamine Stimulation. Leo. J. Meienberg and Charles L. Brown	762
The Incidence and Significance of the Sickle Cell Trait. L. W. Diggs, C. F. Ahmann, and Juanita Bibb	769
Heart Block in the Young. I. I. Lemann	779
Editorial	788
Reviews	791
College News Notes	795
Obituaries	797

Copyrighted by the American College of Physicians

Entered as second class matter at the Post Office, Lancaster, Pa., under Act of March 3, 1879

Eighteenth Annual Clinical Session

THE AMERICAN COLLEGE OF PHYSICIANS

CHICAGO, ILL.—APRIL 16-20, 1934

HEADQUARTERS—THE PALMER HOUSE

In charge of program of general sessions

GEORGE MORRIS PIERSOL, President
1913 Spruce Street, Philadelphia, Pa.

In charge of program of clinics and demonstrations

JAMES B. HERRICK, General Chairman
Peoples Gas Bldg., Chicago, Ill.

COMMITTEE ON CLINICS

ARTHUR R. ELLIOTT, Chairman
30 N. Michigan Ave., Chicago, Ill.

HENRY T. RICKETTS, Graudate School of Medicine, Univ. of Chicago
HUGH A. McGUIGAN, University of Illinois College of Medicine
CHARLES A. ELLIOTT, Northwestern University Medical School
ITALO F. VOLINI, Loyola University School of Medicine
ERNEST E. IRONS, Rush Medical College and Presbyterian Hospital
SOLOMON STROUSE, Michael Reese Hospital
GEORGE W. HALL, St. Luke's Hospital
FREDERICK TICE, Cook County Hospital
ROBERT S. BERGHOFF, Mercy Hospital
JOSEPH BRENNEMANN, Children's Memorial Hospital

Business Management

EDWARD R. LOVELAND, Executive Secretary
133–135 S. 36th St., Philadelphia, Pa.

ANNALS OF
INTERNAL MEDICINE

VOLUME 7 DECEMBER, 1933 NUMBER 6

THE PATHOLOGIC ANATOMY OF THE LIVER IN EXOPHTHALMIC GOITER*

By DONALD C. BEAVER, M.D., and JOHN DEJ. PEMBERTON, M.D.,
Rochester, Minnesota

FOR MANY years icterus has been known as a complication in cases of severe exophthalmic goiter. It has not been demonstrated, however, until fairly recently, that the liver may frequently undergo severe functional and anatomic changes in the syndrome of exophthalmic goiter.

Habershon,[1] in 1874, reported a fatal case of exophthalmic goiter in which jaundice was a complicating feature. Sutcliff,[2] in 1898, observed jaundice in an extraordinarily acute case of exophthalmic goiter. Eder,[3] in 1906, reported three cases of exophthalmic goiter, in each of which jaundice was observed. He commented that Dieulafoy,[4] in 1901, had described the association of jaundice and exophthalmic goiter in his text, "Pathologie interne." Eder considered that the jaundice arose from some chronic intestinal toxemia, as a possible manifestation of the same intoxication which precipitated the exophthalmic goiter. Chvostek,[5] in 1917, referred to the occasional development of icterus in severe cases of "morbus basedowi." He considered its appearance a poor prognostic sign, and concluded that it is of toxic origin. Boothby,[6] in 1922, noted that jaundice was not uncommon in the late stages of long-continued gastrointestinal crises in cases of exophthalmic goiter. He considered it a dangerous sign, and that in most instances it seemed to be an integral part of the syndrome, the direct result of thyroid intoxication. Crotti,[7] in 1922, stated that it "may be observed in a few cases of severe thyrotoxicosis, and that a yellow tint of the sclerotics may rarely be observed in severe, thyrotoxic disturbances of the gastrointestinal tract. He remarked that the prognosis in such cases is always bad, and concluded that the icterus is not due to obstruction of the bile ducts, but is of toxic origin. Assmann,[8] in 1931, stated that signs of hepatic disturbance, especially icterus, may occur in cases of exophthalmic goiter, and that icterus may be present, without having a causal relationship to the exophthalmic goiter, as a manifestation of catarrhal jaundice, and as the result of cholelithiasis, or of inflammatory conditions of the biliary tract. The

* Submitted for publication August 27, 1932.
From the Section on Pathologic Anatomy and the Section on Surgery, The Mayo Clinic.

icterus, however, may be an immediate complication of exophthalmic goiter when there is cardiac decompensation, or it may occur independently of a failing heart as the result of direct toxic influence of the hyperthyroidism. He concluded that icterus, as a complicating symptom of exophthalmic goiter, is found mainly in the most serious cases. The cases, however, do not necessarily terminate fatally.

Evidence to substantiate the intrahepatic origin of the icterus, which also points toward a toxic principle for its etiology, may be found in the literature, based on three types of observation: (1) experimental, (2) clinical evidence of dysfunction of the liver as manifested in the various functional tests for hepatic efficiency, and (3) anatomic changes in the liver.

Farrant,[9] in 1913, by feeding thyroid to cats, guinea pigs, and dormice, reproduced a modified form of the syndrome of exophthalmic goiter resembling the disease of man. He observed, as a rule, fatty degeneration of the livers of central lobular distribution. Kuriyama,[10] in 1918, found that the glycogen content of the liver of animals fed with thyroid is rapidly decreased to a minimum. Cramer and Krause,[11] and others, made similar observations. Hashimoto,[12] in 1921, observed central parenchymal disintegration in livers, varying from simple fatty degeneration to necrosis, in albino rats fed on thyroid in toxic quantities. He also described severe passive congestion, with dismantling of areas about the central veins, sparing only the framework of the liver, and with marked proliferation of Kupffer's stellate cells. He further described regenerative changes in the hepatic cells at the periphery of the affected lobules. In experiments on dogs which were rendered thyrotoxic by feeding desiccated thyroid, Simonds and Brandes,[13] in 1930, found that even though loss of body weight was severe, the liver did not lose weight. Inanition alone, however, produced loss of weight of both liver and body in another group of dogs, the proportional loss of weight being slightly greater for the liver than for the body as a whole. They suggested: "Increased functional activity and increased rate of blood flow are probably important factors in the failure of the liver to lose weight in proportion to the body as a whole, in hyperthyroidism." These observations appear to us not to be directly transferable to cases of exophthalmic goiter, since, as will be observed in the cases we are reporting, the liver was usually small.

Youmans and Warfield,[14] in 1926, established conclusively that hepatic function is impaired in certain cases of thyrotoxicosis. They studied the functional efficiency of the liver by tests of retention, according to the original Rosenthal technic and modifications of it, by levulose tolerance tests, by Widal's hemoclastic crisis test, by computing the icterus index, and by glucose tolerance tests. Cases of adenoma with hyperthyroidism, and of exophthalmic goiter were included in their study. They could observe no relationship between the various clinical factors of the disease and functional impairment of the liver, except loss of body weight. Of 44 cases of thyrotoxicosis studied, there was some impairment of hepatic function in 22 (50

per cent). They were unable to duplicate the results experimentally in dogs to which thyroid extract had been administered. Heilmeyer,[15] in 1931, demonstrated similarly, that by functional tests for hepatic efficiency the function of the hepatic cell was found to be disturbed in half of the cases of exophthalmic goiter which he studied.

References to the changes exhibited by the liver in cases of exophthalmic goiter are not abundant. Askanazy,[16] in 1898, referred to finding a few cases of cirrhosis and a few cases of atrophic nutmeg liver. Marine and Lenhart,[17] in 1911, concluded: "In a significant number of long standing cases coming to autopsy, cirrhosis of the liver has been observed. In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnail. The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well marked fibrous bands. The liver cells usually exhibit some degree of fatty metamorphosis." Pettavel,[18] in 1912, in describing the anatomic pathologic changes in four cases of morbus basedowi, mentioned that in one case the liver revealed evidence of severe stasis, nodular hyperplasia, massive fatty change, and little content of glycogen; in one case marked cirrhosis, moderate content of glycogen and marked peripheral lobular fatty change, and in one case patchy interstitial hepatitis, and fatty degeneration with depletion of glycogen. Matti,[19] in 1912, also found stasis and fatty changes in the livers in cases of morbus basedowi. McCarrison,[20] in 1917, expressed himself as considering the evidences of toxic action on the liver, such as that reported by Marine and Lenhart, as of great importance, and apparently agreed with their statement based on their observations. Kerr and Rusk,[21] in 1922, described a case of hyperthyroidism in which jaundice developed, and at necropsy the liver presented the appearance of extensive destruction, analogous to that of acute yellow atrophy. They considered the hepatic change as a direct expression of the thyrotoxic state. Raab and Terplan,[22] in 1923, reported a case of morbus basedowi with subacute atrophy of the liver. Barker's [23] case, reported in 1930, contained additional evidence of hepatic injury in thyrotoxicosis; in this case the liver was small and necrosis was evident, as also was passive congestion secondary to cardiac failure. Weller's [24] pathologic review of 44 selected cases of exophthalmic goiter, published in 1930, revealed, in addition to acute degenerative changes, the presence of well marked chronic parenchymatous hepatitis in 22 cases, and of slight hepatitis in 16 cases. In only six cases was there no evidence of hepatitis. This is the most extensive review of the subject, from the viewpoint of pathologic anatomy, to be found, and leaves little doubt as to the occurrence of severe hepatic injury in certain cases of exophthalmic goiter. In a second publication on this topic, Kerr [25] stated in 1930 that since the report by himself and Rusk, several other cases had been observed in their clinic; in these cases, the clinical picture was similar, and in the livers of those patients who died, changes were found, similar to those described in the previously reported case. Kerr stated further that in the untreated cases

of exophthalmic goiter of long standing, extensive fibrosis has been observed in the liver, and that this may represent the end stages of changes previously described by himself and Rusk. Lewis,[26] in 1931, reporting from the Lahey Clinic and the Pathologic Laboratory of the New England Deaconess Hospital, concluded that there was no significant anatomic change in the liver in cases of hyperthyroidism, although in one of the 12 cases included in his report, a small liver (960 gm.) was described, which he stated suggested toxic or alcoholic cirrhosis. Assmann, in 1931, considered the most severe stage of toxic injury to the liver in association with exophthalmic goiter to be acute yellow atrophy.

In the investigation to be reported here, a detailed study of the pathologic anatomy of the liver in 107 cases of exophthalmic goiter has been made. The cases were selected, so far as possible, to represent consecutive series over a period of 10 years, excluding from the study only cases of apparent independent hepatic disease, and cases in which other anatomic changes were considered to be possible factors in determining the lesions in the livers. Many of the cases occurred before treatment by iodine was customary, or shortly after such treatment had been introduced. However, the study includes also cases occurring since the time of treatment with iodine.

The clinical history in each case was also carefully reviewed, and correlation of clinical and pathologic features attempted. In order that the pertinent clinical facts of these cases may be appraised, to some extent at least, a summary of the outstanding clinical manifestations will be presented. The cases have been carefully selected to represent only those coming within the designation exophthalmic goiter, as defined by H. S. Plummer.[27]

Clinical Data

The group of 107 cases comprised 35 males and 72 females. This ratio of approximately one male to two females in this group is not quite the same as the ratio of one male to 2.48 females with exophthalmic goiter registered at The Mayo Clinic for the same period of years. The average age of the patients in our series was 44.63 years; for the males the average was slightly higher than this, 49.22 years, and for the females slightly lower, 42.40 years. The average age of patients presenting themselves at The Mayo Clinic for treatment of exophthalmic goiter in the same period was approximately 39 years, 41.6 years for the males and 38 years for the females. The extremes of age in our series of cases were 14 and 72 years.

The average duration of exophthalmic goiter in our series was 2.53 years. This differs from an average duration of approximately 1.5 years for all cases of exophthalmic goiter in the same period. The cases were graded as to severity in terms of clinical manifestations of the disease, on the basis 1 to 4, all factors being considered. This phase of the investigation was prepared from the data obtained at the time of examination, and did not take into consideration subsequent changes in severity of the disease, nor

did it consider the type of death unless complicating factors were such as to exclude the case from this study. Such consideration placed the average severity, represented numerically, at 2.75. In only two cases was hyperthyroidism graded 1; in 34 cases it was graded 2; in 56, 3, and in 15 cases, 4. In 26 of the cases (24 per cent), thyroid crisis or verge of crisis was noted, as judged by the severity of the thyroid reaction, cases of postoperative thyroid reaction being excepted. Of the patients with crisis, 20 were females and six, males. The average basal metabolic rate in 95 cases in which it was recorded was + 66 per cent. The lowest and highest rates were respectively + 16 per cent and + 127 per cent. The averages were computed on the basis of highest recorded rate. The average weight of the patients, based on 105 cases in which accurate weights were taken not long before death, was 117 pounds. For the females it was 111 pounds, and for the males, 126 pounds. The lowest recorded weight was 56 pounds and the highest, 180 pounds. The loss of body weight for the group as a whole was 23.9 per cent; of the females it was 22.8 per cent and of the males, 25.14 per cent.

Twenty-three patients (21.5 per cent) had icterus, which was graded by clinical objective estimation from 1 to 4, as follows: in 17 cases the icterus was graded 1; in four cases, 2; in one case, 3; and in one case, 4. In the 17 cases in which icterus was graded 1, the color was frequently observed only in the sclerotics, or it was only icteroid, but in the six cases in which it was graded 2 to 4 it was well defined to extreme.

Pathologic Data with Clinical Correlation

Two outstanding types of hepatic change were observed: acute, and chronic. The acute changes were characterized by fatty metamorphosis, and central or focal necrosis. Frequently more than one of the acute changes were observed in the same liver. The chronic changes consisted of two prominently displayed types of lesions; namely, simple atrophy, and toxic subacute atrophy which in some instances had progressed to actual cirrhosis. The chronic lesions were frequently so blended that all stages and types could be observed in the various preparations of the same liver; in other cases they were distinctly individual. Frequently, both acute and chronic hepatic lesions were found in the same case.

Acute Degenerative Hepatic Lesions. Such lesions appeared in all but nine of the 107 cases; that is, in 91.5 per cent. Their type, grade, and frequence are recorded in table 1. In many cases, more than one type of acute lesion was seen in the same liver, thus accounting for the apparently discordant percentages.

With certain reservations, we agree with Weller's conclusion in respect to the significance of the acute lesions. He stated: "It is impossible to attach much importance to such changes because of their very frequent occurrence in a variety of conditions other than thyrotoxicosis." On the other hand, it is impossible completely to ignore them in the face of such a

TABLE I

Acute Degenerative Changes of Liver, 107 Cases of Exophthalmic Goiter

Type of Change	Grade 1	2	3	4	Total	Per cent
Fatty changes	53	26	13	2	94	87.8
Central necrosis	31	18	4	1	54	50.4
Focal necrosis	4	2	1	0	7	6.5

A total of 98 cases (91.5 per cent) revealed acute changes.

high percentage of association. From experimental evidence their importance seems confirmed; also, from the fact that they have been the most frequently described hepatic lesions in cases of exophthalmic goiter. Of particular significance in this series is the large number of cases exhibiting actual necrosis, either central or focal (50 and 6.5 per cent, respectively). The occurrence of such changes, especially the more severe changes, may be of considerable importance in the evolution of chronic changes to be described, as well as directly contributing to hepatic dysfunction itself.

It is unnecessary to present a detailed microscopic description of the fatty changes, for the picture was the usual one seen in fatty metamorphosis of the liver. This change was often severe. It usually occupied the central lobular region, although in some instances it was peripheral. When the change was severe, almost all of the cells of the lobule were affected. In some cases one microscopic field would present the picture of simple fatty change, and in another field central or focal necrosis could be seen.

Actual necrosis, either of focal or central type, appeared microscopically so frequently that it seemed to represent an accentuation of the same toxic reactions which usually resulted in fatty metamorphosis sometimes progressing to necrosis.

Microscopic examination of the zones of necrosis revealed hyaline thrombosis of the lobular sinusoids, with necrosis of hepatic cells, and usually with fairly definite collections of polymorphonuclear leukocytes. In some instances, however, the necrosis seemed to appear without these changes. In these zones, hyaline, granular, cytoplasmic retrogressions, with various nuclear degenerations or complete nuclear lysis were found, which resulted in dismantling of hepatic cells of the regions of the central vein, with only sinusoidal reticulum remaining. The latter change is the type which more frequently characterizes the necrosis of hepatic cells of idiopathic acute yellow atrophy of the liver. In five cases, the hepatic degenerative lesions were sufficiently severe to pass for the changes of moderately severe acute yellow atrophy of the liver. The milder changes were apparently of the same pathogenesis; differences were a matter of degree.

In 13 cases there was evidence of fairly well defined stasis of blood in the livers, with the resulting hepatic parenchymal disturbances usually found in passive congestion of the liver. In no instance was the change diffuse,

but appeared only in isolated areas. It occurred independently, or in conjunction with the necrotic lesions already described. In only a few instances, however, did it appear to be directly connected with their pathogenesis, although probably the acute lesions were accentuated when passive congestion was severe. Similar acute lesions, however, appeared without congestion.

In consideration of clinical factors relating to exophthalmic goiter, which possibly could influence the development of acute hepatic lesions, the following facts have been adduced. No relationship could be found between age of the patient, sex, or percentage loss of body weight and the occurrence of the acute hepatic lesions. With the exception of loss of body weight, the hepatic lesions appeared to be directly in proportion to the severity of hyperthyroidism, as graded (all factors being considered), or as expressed by individual criteria such as crisis or basal metabolic rate. In the two cases of hyperthyroidism graded 1, 50 per cent of the livers revealed acute degenerative changes; in the 31 cases of hyperthyroidism graded 2, 29 per cent of the livers revealed evidences of acute changes; in 52 cases of hyperthyroidism, graded 3, 48 per cent of the livers had acute lesions, and in the 15 cases of hyperthyroidism graded 4, 100 per cent of the livers exhibited acute changes. The high proportion of acute degenerative changes in cases graded 1 may be on the basis of insufficient numbers. In all cases in which there was crisis, or in which the patients were on the verge of thyroid crisis (26 cases), there were acute hepatic lesions; the hepatic lesions, graded as to severity, occurred as follows in the cases with crisis: 30.8 per cent, grade 1; 38.5 per cent, grade 2; and 30.7 per cent, grade 3. Of 38 cases in which there was a basal metabolic rate of + 60 per cent or less, in 18 per cent the livers were without acute lesions, whereas in 57 cases in which the basal metabolic rate was more than + 60 per cent, in only two cases (3.5 per cent) were acute hepatic lesions absent. The more severe acute degenerative hepatic lesions were in the cases in which hyperthyroidism was of relatively short duration; 64 per cent of the acute hepatic changes occurred in cases of duration of one year or less. This is in contrast with the average duration of exophthalmic goiter for the entire number of cases, which was 2.53 years. The fact that most of the cases of exophthalmic goiter of duration of one year or less were the more severe, coincides with the fact that severity of the exophthalmic goiter is the principal factor influencing the development of acute degenerative lesions of the liver.

Chronic Atrophy. Atrophy was the most conspicuous, and also possibly the most important hepatic lesion observed. It is impossible to consider atrophy independently of other changes, because of the frequent association of acute changes and other chronic changes in the livers which exhibited atrophy. Nevertheless, the other lesions may be temporarily disregarded, with the understanding that the aspect under consideration is not pathogenesis, but atrophy in a broad, descriptive sense. By the term atrophy we refer to loss of weight of the organ.

More data must be obtained on the normal weight of the liver of human beings, as influenced by age, sex, body weight, stature, or nutritional factors. Until these data have been assembled, a conclusive statement cannot be made concerning the normal weight of the liver. Jackson [28] gave the normal average weight of the liver as 1,500 gm., with variability from 1,000 to 2,000 gm., and according to him the weight of the liver is 2.5 per cent of that of the body of a man, and a somewhat higher percentage of that of the body of a woman. Gray's [29] figures for the adult were 1,417 to 1,700 gm. for men and 1,134 to 1,417 gm. for women, constituting about one thirty-sixth of the entire body weight. Vierordt's [30] figures were 1,801 gm. for men at the age of 25 and 1,648 gm. for women at the same age; he gave the percentage of hepatic weight to body weight as 2.75.

Notwithstanding the extreme variability in the weight of the liver, as expressed in the preceding figures, the livers in our series of cases of exophthalmic goiter were usually below the average normal. The average weight of the liver for the entire series of cases was 1,316 gm.; for the male it was 1,451 gm., and for the female it was 1,252 gm. The extremes were 644 and 2,450 gm. Curiously enough, the smaller of these two livers revealed only simple atrophy, with slight increase of connective tissue, and the larger advanced cirrhosis with nodular regeneration. The approximate weights of the livers in our 107 cases are given in table 2. It would seem

TABLE II

The Weight of the Livers

Weight of Liver, gm.	Cases
600 to 700	1
700 to 800	3
800 to 900	4
900 to 1000	7
1000 to 1100	8
1100 to 1200	13
1200 to 1300	11
1300 to 1400	21
1400 to 1500	9
1500 to 1600	14
1600 to 1700	6
1700 to 1800	3
1800 to 1900	2
1900 to 2000	2
2000 to 2100	1
2100 to 2200	1
2200 to 2300	0
2300 to 2400	0
2400 to 2500	1
Total	107
Average weight of liver	1316 gm.
Average weight of liver, females	1252 gm.
Average weight of liver, males	1451 gm.

In 68 cases (63.55 per cent) weight of liver was less than 1400 gm.

to be a conservative assumption that a liver of any adult human being, including both sexes, which weighs less than 1,400 gm., represents atrophy. Presuming this to be true, there are 68 cases (63.55 per cent) in this series in which the liver was atrophic.

When the acute degenerative lesions, and lesions of moderate to moderately severe cirrhosis were excluded, there was little microscopic structural alteration from normal in the atrophic livers. In some, however, simple atrophy appeared, in that the hepatic cells were uniformly small, or small only about the central veins, with slight if any increase in connective tissue. In others there was moderate increase in connective tissue about the periportal spaces, with sometimes condensation of periportal structures, so that from four to six or more units appeared in one low power (16 mm.) microscopic field (figure 1). In other fields this change was limited to the

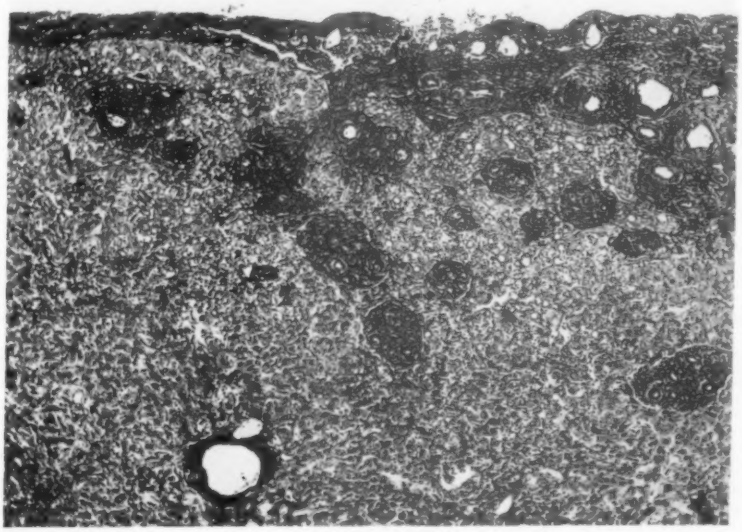


FIG. 1. Atrophy with prominent periportal units.

hepatic tissue beneath Glisson's capsule. Some zones contained streaks or bands of atrophic hepatic cords appearing to connect central and portal veins, or two adjacent portal veins (figure 2). In the apparently older lesions complete atrophy of certain cords left threads or narrow bands of increase of connective tissue within the lobules (figure 3), around the periportal connective tissue, or extending between two periportal areas. These changes were regarded as those of simple parenchymal atrophy, although it was not always possible to exclude the influence of acute degenerative changes in their pathogenesis.

The factors which, in relation to the syndrome of exophthalmic goiter, could have brought about the loss of weight of the livers, may be adjudged

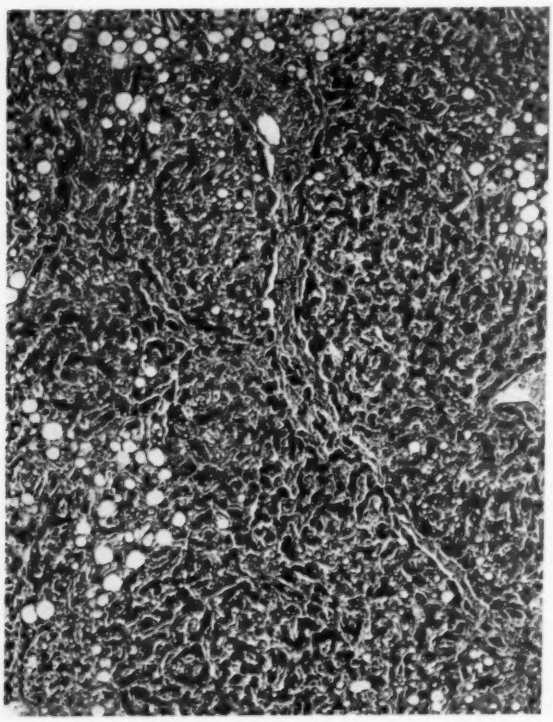


FIG. 2. Streaks or bands of atrophic hepatic cords.

FIG. 3. Atrophy with threads or bands of connective tissue replacing atrophic hepatic cords.

by subjecting the anatomic considerations to analysis on the basis of clinical variations. The correlation is rendered difficult because of the frequent association of other pathologic conditions of the liver, which in themselves could have influenced the weight of the organ. Even though the other changes resulted from the syndrome of exophthalmic goiter, the conditions bringing them about may have been somewhat different.

The influence of sex has already been stated; the livers of women were, on the average, 199 gm. lighter in weight than those of men. Although the changes according to age were not marked, there was a general tendency for falling off of the hepatic weights from the age of 25 to 30 years, at which the maximal average weight was 1,512 gm., to the age of 70 to 75 years, at which the minimal average weight was 1,096 gm. This decline is graphically revealed in figure 4. There were no significant changes in hepatic

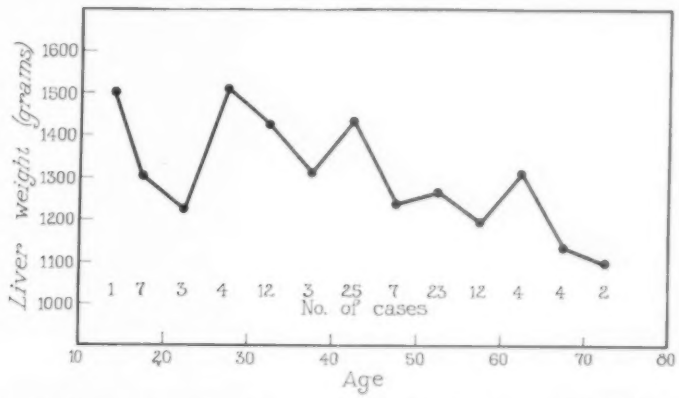


FIG. 4. Influence of age on the weight of the liver in exophthalmic goiter.

weights when compared with the duration of the hyperthyroid state. Compared with the clinical severity of hyperthyroidism as graded on the basis of all clinical factors, the decline in hepatic weight was proportional to the increase in severity. In the two cases of grade 1 the average hepatic weight was 1,150 gm.; in the 34 cases of grade 2 it was 1,418 gm.; in the 56 cases of grade 3 it was 1,293 gm., and in the 15 cases of grade 4 it was 1,194 gm. Since there were only two cases of hyperthyroidism of grade 1, one in which there was a relatively large liver, and one in which it was relatively small, little significance can be attached to the exception grade 1 offers to the trend of decrease in hepatic weight in proportion to intensity of hyperthyroidism. In the 26 cases in which there was thyroid crisis or in which the patients were on the verge of crisis, the average hepatic weight was 1,289 gm. as compared with 1,316 gm. for the entire group. No correlating factors could be determined between hepatic weight and basal metabolic rate. The smaller livers were usually found in bodies of which the weights were relatively small at death, and the larger livers in bodies of greater weight. This relationship is graphically shown in figure 5. These data, however, are not

exceedingly useful, since the same relationship probably exists normally. The percentage of loss of body weight has not been computed against the estimated percentage of loss of hepatic weight, due to inability so far to agree on the normal ratio of weight of liver to weight of body. It is obvious that percentage loss of body weight could not be compared with the weight of the liver at death, without consideration being given for the weight of the liver before loss of body weight occurred. A continuation of this phase of the investigation is contemplated. That the weight of the liver usually remains in a relatively normal ratio to the weight of the body at the time of death does not lessen the argument in favor of the loss of hepatic weight

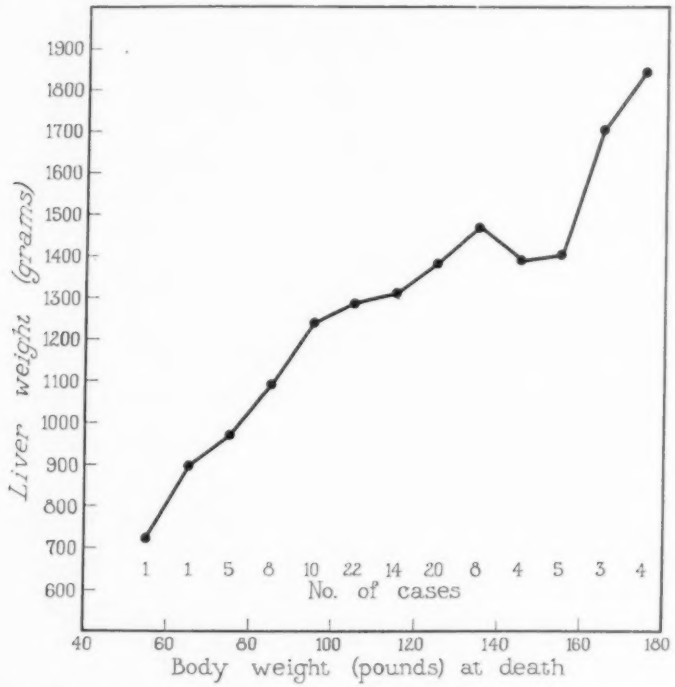


FIG. 5. Relationship of body weight at death to hepatic weight, in exophthalmic goiter.

being the result of the state accompanying exophthalmic goiter. Both loss of hepatic weight and loss of body weight occur, each being related to the syndrome of exophthalmic goiter, and each relatively proportional to the intensity of the disease, in both instances apparently to about the same degree.

In summarizing, three clinical factors seem important in determining the weight of the liver: (1) age of the patient, (2) weight of body at the time of death, and (3) intensity of the disease.

Chronic Cirrhosis. The development of cirrhosis of the liver in cases of exophthalmic goiter is intimately concerned with the lesions already described. Its pathogenesis appeared to be, in part, on the basis of toxic

changes, and in part on the basis of simple atrophy. The changes of cirrhosis are the terminal stages, or nearly the terminal stages of these lesions. Since the factors of etiology were variable in severity, so also were the lesions which contributed to the cirrhosis, and the lesions of cirrhosis themselves. Thus, varying grades of cirrhosis may be described, grading imperceptibly into the lesions which were pathogenetically related to them. In most instances these changes were progressive, corresponding to subacute or early chronic, toxic atrophy of the liver. In fact, in only one case could the lesion be considered completed and indistinguishable from ordinary atrophic cirrhosis. In table 3 these lesions have been graded, and per-

TABLE III

Chronic Hepatic Lesions of Cirrhotic Type

Grade	Number of Cases	Per cent	Average Weight of Liver, gm.
1	48	44.86	1320 (extremes 644 to 2177)
2	13	12.15	1180 (extremes 809 to 1633)
3	2	1.87	1591 (extremes 1100 to 2450)
4	1	0.93	1100
Total	64	59.81	1364

centages for each grade are given. The lesions of grade 1 are those of slight degree, which could hardly be classified as of sufficient development really to constitute cirrhosis. Considering all grades of lesions, this change appeared in 59.81 per cent of the cases, but of more significance is the 14.95 per cent, comprising the cases of cirrhosis of grades 2, 3, and 4, obviously much higher than that found in general material submitted to necropsy. In the material representing grades 2, 3 and 4 the lesions were moderately severe to well advanced.

The microscopic pathologic changes in the cases of cirrhosis in this series were almost identical with the description presented by Weller for his cases. He called the condition interlobular chronic parenchymatous hepatitis, and wrote concerning it as follows: "This is characterized by lymphocytic infiltration, bile duct proliferation and increased stroma in the islands of Glisson. From the usual form of atrophic cirrhosis this picture differs, however, in being much more irregularly distributed in the liver and also in respect to the slight intralobular distribution at the periphery of the lobule, present in the more advanced cases."

The microscopic anatomic changes, presented in detail for the entire 64 cases of cirrhosis, with particular emphasis on the 16 cases in which changes were moderate to severe, revealed a general tendency to increase in connective tissue, either relative or real. The connective tissue was not only extremely variable in amount and in anatomic position of its localization (figure 6), but also extremely variable in its occurrence, from one portion of the liver to another. However, the larger amounts were usually to be found

within or surrounding the periportal spaces, and encroaching to some extent on the periphery of the lobule. In other instances the connective tissue could be identified throughout the lobule, where normal hepatic cords barely persisted in sufficient numbers to identify the lobular unit (figure 7). Or, it was found in the form of perivenous fibrosis about the central veins, or less marked, as small, thread-like bands of connective tissue extending irregularly from the central vein, interposed between the hepatic cords. It sometimes connected the region of the central vein with the portal vein as a connective tissue band, and at other times extended between two contiguous portal

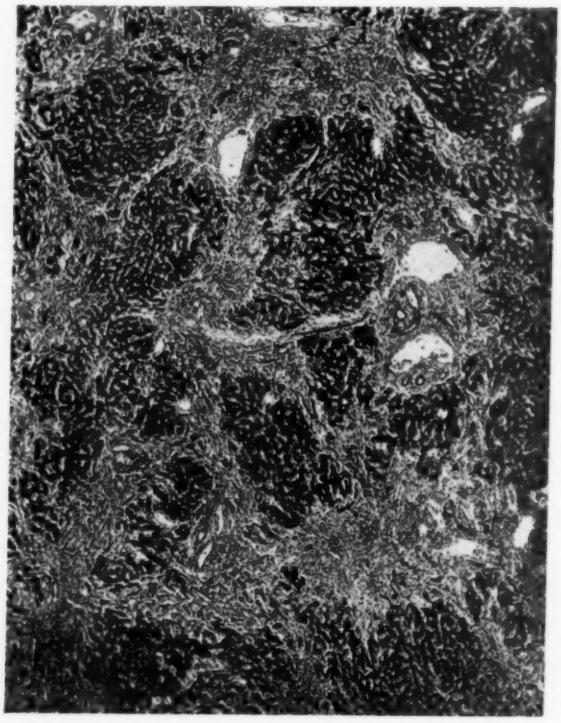


FIG. 6. Irregular fibrosis and atrophy of hepatic parenchyma.

spaces. In the older stages, the position of the connective tissue was often modified by the regenerative nodules of hepatic parenchyma, and only in such cases did it possess a definite perilobular or monolobular distribution (figure 8). Since in the earlier cases we were dealing with cirrhosis in the making, this fact seems significant in the pathogenesis of ordinary cirrhosis, especially in consideration of the connective tissue found in the terminal stages. The connective tissue was usually found to contain a considerable number of lymphocytes. In the connective tissue zones "bile duct" forms were frequently found in increased numbers; on the other hand, they might be entirely absent. Regeneration of hepatic parenchyma was usually not a

prominent feature in these cases, although in some the regeneration of parenchyma, as well developed nodular formations (adenomas), was observed.

Certain factors had possible influence on the development of chronic cirrhosis, from the standpoint of exophthalmic goiter. Analysis and correlation of the clinical factors will be applied only to the cases in which cirrhosis was graded 2, 3 or 4, because of the mildness of the lesions in those listed as of grade 1. Nine of the 16 patients were women, and seven, men. The average age of the patients with cirrhosis was 52.06 years; of the

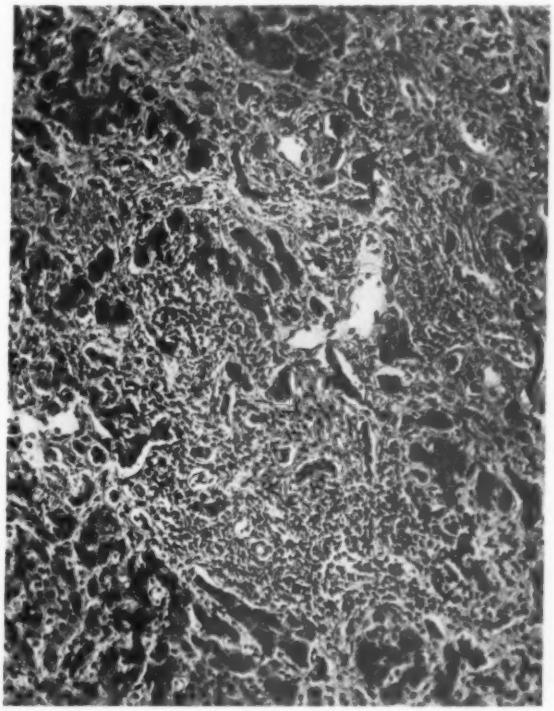


FIG. 7. Atrophic cords of hepatic cells with irregular fibrous replacements.

women, 53.40 and of the men 48.83 years. The extremes of age were 39 and 66 years. This is in contrast with the average age for the entire group of cases, which was 44.63 years, with extremes of 14 and 72 years. The average duration of hyperthyroidism in cases of cirrhosis was three years and ten months, with extremes of six months and 10 years, whereas for the group as a whole it was 2.53 years, and 64 per cent of the acute hepatic lesions appeared in cases of hyperthyroidism of one year or less in duration. The average severity of hyperthyroidism in this series was 3 (graded on the basis of all factors) in contrast with 2.75 for the entire group. Crisis was a clinical manifestation in only five of these cases. The average basal me-

tabolic rate was + 80.75 per cent as contrasted with + 66 per cent for all cases. Percentage loss of body weight in this group was slightly higher than the average of 23.9 per cent for the entire study. In the cases of cirrhosis the loss was 29.18 per cent; for the women 30.70 per cent and for the men 27.11 per cent. Icterus was present in seven of the 16 cases.

From anatomic consideration, the livers in the cases of chronic cirrhosis presented an average weight of 1,258 gm. (1,160 gm. for the women and 1,440 gm. for the men) with extremes of 809 and 2,450 gm. This is somewhat less than for the entire series, in which the average hepatic weight

FIG. 8. Atrophic cirrhosis with nodules of regenerated hepatic parenchyma surrounded by fibrous connective tissue.

was 1,316 gm. Average weight of the spleen in the group with cirrhosis was 245 gm., with variation between 100 and 550 gm. Ascites was present in five cases, but its development was usually terminal, possibly dependent on factors of terminal failing cardiac compensation; too much emphasis cannot be placed on this finding.

Summarizing these data reveals that cirrhosis appears among older patients, with diseases of longer duration and of greater than average severity. These data pertaining to the cases of cirrhosis have been summarized in table 4.

TABLE IV

Moderate and Severe Cirrhosis and Associated Clinical and Anatomic Findings

Case	Age, Years, and Sex	Cirrhosis		Clinical Grade of Exophthalmic Goiter	Duration of Exophthalmic Goiter	Basal Metabolic Rate, Per cent	Crisis	Loss of Body Weight, Per cent	Jaundice	Weight of Liver, gm.	Ascites	Weight of Spleen, gm.
		Grade 2	Grades 3 and 4									
19	46F	+	−	3	5 yrs.	+102	0	22	0	1025	0	162
20	50F	+	−	4	2 yrs.	+ 91	+	36	+	1525	0	325
24	59M	+	−	3	6 mo.	+ 73	0	14	+	1600	0	125
30	39M	−	+	4	2 yrs.	—	0	29	+	1225	3000 c.c.	550
31	52M	+	−	3	6 yrs.	+ 44	0	49	+	1300	1500 c.c.	230
32	59F	+	−	3	14 mo.	+104	0	30	0	975	3000 c.c.	100
38	66F	+	−	3	6 yrs.	+ 98	0	50	0	900	0	120
42	63M	+	−	3	15 mo.	+ 61	0	37	+	809	3000 c.c.	180
56	43F	+	−	4	5 yrs.	—	+	26	+	1005	0	257
58	40M	−	+	4	5 yrs.	+102	+	6	+	2450	0	515
64	63F	+	−	4	10 yrs.	+114	+	12	0	1100	0	110
65	57F	+	−	3	1 yr.	—	+	29	0	1425	0	200
85	52F	−	+	1	5 yrs.	+ 38	0	23	0	1100	0	205
99	42M	+	−	3	11 mo.	+ 73	0	40	0	1633	0	395
105	56M	+	−	3	3.5 yrs.	+ 69	0	37	0	957	0	292
106	46F	+	−	2	3 yrs.	—	0	27	0	1100	1000 c.c.	160
Total or average	52	13 (12 per cent)	3 (2.8 per cent)	3+	3 yrs. 10 mo.	+ 80.75	5	29	7	1258	5 cases	245

Icterus in Association with the Acute and Chronic Lesions. With the clinical discussion, mention has been made of the occurrence of icterus, but because of its pathologic importance brief consideration will be given, to facilitate its interpretation. It should be remembered that cases which were thought to represent previous or independent hepatic or biliary obstructive disease were excluded from this study, so that icterus on that basis need not be considered here. The data concerning icterus are summarized in table 5.

Icterus occurred in 23 cases (21.5 per cent) of this series; 10 of the patients were males and 13, females. It was of moderate to extreme grade in six cases and mild in 17. The average age of the patients who exhibited this change was 48.17 years, as compared with 44.63 years for all cases. For the males the average age was 56 years, and for the females, 42.15 years. Icterus was observed in the more severe cases. As judged by all clinical criteria, it appeared in cases with an average severity of grade 3, as compared with severity of grade 2.75 for the entire study. The average duration of hyperthyroidism in the cases in which there was icterus was not materially different than for the entire study; namely, 2.38 years as compared with 2.53 years. Seven patients with icterus were in, or on the verge of, thyroid crisis before death. The basal metabolic rate was exactly the same for the cases with icterus as for the entire number of cases. The percentage loss of body weight was 29.52 per cent in the series with icterus, as compared with 23.9 per cent for the cases as a whole.

The average hepatic weight, in cases in which jaundice was a clinical manifestation, was essentially the same as for the entire study, 1,348 gm. compared with 1,316 gm. Cirrhosis was present to some degree, although usually slight, in 19 of the 23 cases. It was graded 1 in 12 cases, and 2 or 3 in seven cases (30.4 per cent). Acute degenerative lesions were present in all cases. The changes were (1) fatty metamorphosis in 21 cases, graded 1 in nine cases, 2 in six cases, and 3 in six cases, and (2) focal or central necrosis, or both, in 18 cases, graded 1 in eight cases, and 2 or 3 in ten cases. In cases 6, 35, 77 and 81 (table 5) the hepatic changes, as judged anatomically, appeared not to be of sufficient severity to account for icterus, although mild changes existed in these cases.

In consideration of all cases from the viewpoint of probable hepatic dysfunction, whether icterus was present or not, it was estimated that lesions of sufficient severity to reveal hepatic dysfunction by dye tests or other tests of hepatic function existed in approximately 40 per cent of the cases; this estimate compared favorably with the figure of 50 per cent recorded by Youmans and Warfield who actually applied these tests. This phase of the subject, tests for hepatic function, is being investigated at present and will be reported subsequently.

Of interest, and of possible significance, was the mild to rather intense accumulation of bile pigment in the hepatic cells of the central lobular zones, in cases with or without jaundice, indicating the inability of the hepatic cells

TABLE V

Correlation of Icterus and Clinical and Anatomic Findings

Case	Age in Years, and Sex	Jaundice, Grade	Duration of Exophthalmic Goiter	Clinical Grade of Exophthalmic Goiter	Basal Metabolic Rate, Per cent	Loss of Body Weight, Per cent	Crisis	Weight of Liver, gm.	Cirrhosis of Liver, Grade	Fatty Change, Grade	Central Necrosis, Grade	Focal Necrosis, Grade
1	52M	1	10 yrs.	3	+ 67	30	0	1100	1+	2	0	0
6	14F	1	9 mo.	2	+ 31	7	0	1500	0	1	0	0
20	50F	2	2 yrs.	4	+ 91	36	+	1525	2	2	0	0
24	59M	3	6 mo.	3+	+ 73	14	0	1600	2	3	2	0
28	15F	1	9 mo.	4	+ 61	48	0	1725	0	1	2	0
30	39M	2	2 yrs.	4	—	29	0	1225	3	1	3	2
31	52M	2	6 yrs.	3	+ 44	49	0	1300	2+	1	1	0
35	38F	1	8 mo.	3	+102	39	0	1500	1	0	1	0
76	40F	1	5 yrs.	3	+ 93	23	+	1200	1	2	1	0
77	58M	1	4 mo.	2	+ 61	36	0	1675	1	1	0	0
78	66M	1+	8 mo.	3	+ 64	28	0	1300	1	2+	1	0
81	40F	1	3 mo.	2	+ 31	8	0	1193	0	0	1	0
82	74M	1	2 yrs.	2	+ 42	29	0	1395	1	2+	2	2
83	54F	1	1 yr.	3	+ 32	29	+	1088	1	3	3	3
93	43F	1+	10 mo.	3	+ 83	25	0	1840	1	3	2	0
95	57M	1	1 yr.	4	+ 80	40	+	1090	0	1	2	1+
41	42F	1+	6 mo.	3	+ 54	44	+	1520	1+	3+	1+	0
42	63M	1	15 mo.	3	+ 61	37	0	809	2	1	2	0
44	58F	1	3 mo.	3	+ 80	37	0	794	1	2	2	0
56	43F	4	5 yrs.	4	—	26	+	1005	2	1	1	0
58	40M	1	5 yrs.	4	+102	6	+	2450	3	3	0	0
66	52F	2+	8 yrs.	3	—	*	0	1270	1	3	3+	0
107	59F	1	14 mo.	3	—	?	0	952	1+	3	1	0
Total or average	48+	17	2.3 yrs.	3+	+ 66	29.52	7	1348	19	21	18	4

* Emaciation, graded 4.

to excrete satisfactorily, with consequent accumulation of biliary pigments in the functionally impaired hepatic cells. In no instance was anatomic obstruction to flow of bile a part of the picture.

Five of the cases of icterus were associated with passive congestion of the liver of relatively severe grade. In case 35, not having any other adequate explanation, this finding could be used to explain the icterus, for it is known that passive congestion of the liver and icterus may be associated conditions. In the remaining cases, passive congestion is not needed to explain the icterus, unless one indirectly considers that the passive congestion favored the formation of other anatomic changes in the liver, which in themselves were sufficient to account for its occurrence.

In summarizing, we may state that the anatomic explanation for the occurrence of icterus usually rests on the basis of clearly demonstrable alterations of hepatic tissue. In four cases only was this anatomic explanation considered inadequate. Icterus seems to occur in two types of cases, in both of which atrophy is the outstanding condition: (1) cases of shorter but more severe hyperthyroidism in which atrophy and acute toxic changes predominate, and (2) cases of longer, relatively less severe hyperthyroidism, in which terminal acute changes are superimposed on a liver exhibiting atrophy and some degree of cirrhosis.

Summary and Conclusions

Analysis was made of the pathologic anatomy of the liver and the correlated clinical findings in 107 cases of exophthalmic goiter.

Three types of hepatic lesions predominate in exophthalmic goiter: (1) acute degenerative lesions (fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood); (2) simple atrophy, and (3) subacute toxic atrophy and toxic cirrhosis.

The frequency of these lesions was as follows: (1) acute lesions 91.5 per cent, of which fatty metamorphosis composed 87.8 per cent, central necrosis 50.4 per cent, and focal necrosis 5.6 per cent; (2) atrophy 63.55 per cent, in which cases the average weight of the liver was 1,316 gm., and (3) subacute toxic atrophy and cirrhosis 59.81 per cent, of which lesions of grade 1 composed 44.86 per cent, lesions of grade 2, 12.15 per cent, lesions of grade 3, 1.87 per cent, and lesions of grade 4, 0.93 per cent.

Jaundice was present in 23 cases (21.5 per cent). The hepatic lesions are usually adequate to account for the presence of icterus, and in addition, including cases without jaundice, they are sufficient probably to cause disturbances of hepatic function detectable by clinical tests of hepatic efficiency in approximately 40 per cent of the cases.

The common factor in the evolution of these lesions appears to be severity of the syndrome of exophthalmic goiter.

The acute lesions are not usually influenced in their occurrence or severity by the age of the patient, the sex, or the percentage loss of body weight. Except for the loss of body weight, the acute lesions usually occur

directly in proportion to severity of the disease. They appear most prominently in the more severe cases of shorter than average duration.

Atrophy is more pronounced among females than males, and appears to be more marked among the aged than the young. It is proportional to severity of the disease, with the exception that it seems not to be correlated with basal metabolic rate. The duration of the disease does not appear to be a factor. The smaller livers were observed in the smaller subjects, and the larger livers in the larger subjects. The relationship of the weight of the liver to loss of body weight, however, will constitute an independent study.

The changes of subacute toxic atrophy and cirrhosis appear more frequently among females than males but the difference in incidence, according to sex, is not greater than in the entire study. These lesions appear among older patients, among whom the disease is of longer duration and of more than average severity.

We may conclude, as Boothby did in speaking of jaundice in exophthalmic goiter, that in most instances the lesions in the liver appear to be an integral part of the syndrome of exophthalmic goiter, and that they are due directly to thyroid intoxication, since, as we have found, they are usually intimately related in their severity, to the intensity and the duration of the disease. It is probable that the hepatic changes are not only related to the hyperthyroid state, but also to the toxic factor of exophthalmic goiter, which Plummer believes exists, for in experimentally produced hyperthyroidism, induced in animals by feeding thyroid substance, lesions comparable to those we have described have not been produced. Atrophy, acute degeneration, and cirrhosis are probably interrelated conditions, each with a sequential pathogenetic relationship to the other, and each intimately concerned with the hyperthyroid state and the toxic factors as elaborated in the syndrome of exophthalmic goiter.

BIBLIOGRAPHY

1. Habershon, S. O.: Exophthalmic goiter; heart disease; jaundice; death, Lancet, 1874, i, 510.
2. Sutcliff, E. H.: An extraordinarily acute case of Graves' disease, Lancet, 1898, i, 717.
3. Eder, M. D.: Three cases of jaundice occurring in persons suffering from exophthalmic goiter, Lancet, 1906, i, 1758.
4. Dieulafoy, G.: Quoted by Eder.
5. Chvostek, F.: Morbus Basedowi und die Hyperthyreosen, 1917, Julius Springer, Berlin.
6. Boothby, W. M.: Part 4. Diagnosis and treatment of the diseases of the thyroid gland, 1922, Oxford Medicine, Oxford University Press, New York, iii.
7. Crotti, A.: Thyroid and thymus, 1922, Lea and Febiger, Philadelphia.
8. Assmann, H.: Leber und Milz bei Morbus Basedow, München. med. Wchnschr., 1931, lxxviii, 221–225.
9. Farrant, R.: Hyperthyroidism: its experimental production in animals, Brit. Med. Jr., 1913, ii, 1363–1367.
10. Kuriyama, S.: The influence of thyroid feeding upon carbohydrate metabolism. I. The storage and mobilization of the liver glycogen in thyroid-fed animals, Jr. Biol. Chem., 1918, xxxiii, 193–205.

11. CRAMER, W., and KRAUSE, R. A.: Carbohydrate metabolism in its relation to the thyroid gland; the effect of thyroid feeding on the glycogen con'ent of the liver and on the nitrogen distribution in the urine, Proc. Roy. Soc. London, Series B, 1913, lxxxvi, 550–560.
12. HASHIMOTO, H.: Heart in experimental hyperthyroidism with special reference to its histology, Endocrinology, 1921, v, 579–606.
13. SIMONDS, J. P., and BRANDES, W. W.: Effect of experimental hyperthyroidism and of inanition on heart, liver and kidneys, Arch. Path., 1930, ix, 445–460.
14. YOUMANS, J. B., and WARFIELD, L. M.: Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency, Arch. Int. Med., 1926, xxxvii, 1–17.
15. HEILMEYER, L.: Blutfarbstoffwechselstudien. 3. Mitteilung: Blutmauserung und Leberfunktion beim Morbus Basedow, Deutsch. Arch. f. klin. Med., 1931, clxxi, 515–528.
16. ASKANAZY, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung, Deutsch. Arch. f. klin. Med., 1898, lxi, 118–186.
17. MARINE, D., and LENHART, C. H.: Pathological anatomy of exophthalmic goiter: the anatomical and physiological relation of the thyroid gland to the disease; the treatment, Arch. Int. Med., 1911, viii, 265–316.
18. PETTAVEL, C. A.: Beitrag zur pathologischen Anatomie des Morbus Basedowii, Deutsch. Ztschr. f. Chir., 1912, cxvi, 488–543.
19. MATTI, H.: Quoted by Chvostek.
20. MCCARRISON, R.: The thyroid gland in health and disease, 1918, Wm. Wood and Company, New York.
21. KERR, W. J., and RUSK, G. Y.: Acute yellow atrophy associated with hyperthyroidism, Med. Clin. N. Am., 1922, vi, 445–459.
22. RAAB, W., and TERPLAN, C.: Morbus Basedowii mit subakuter Leberatrophie, Med. Klin., 1923, xix, 1154–1156.
23. BARKER, L. F.: Thyreo-intoxication with necrosis and atrophy of liver, damage to heart muscle and kidneys, and terminal bronchopneumonia, Med. Clin. N. Am., 1930, xiv, 261–263.
24. WELLER, C. V.: Hepatic lesions associated with exophthalmic goiter, Trans. Assoc. Am. Phys., 1930, xlv, 71–76.
25. KERR, W. J.: Necrosis of heart and liver in thyrotoxicosis, with some notes on possible changes in other organs, Northwest Med., 1930, xxix, 430–431.
26. LEWIS, W.: Hyperthyroidism and associated pathology, Am. Jr. Med. Sci., 1931, clxxxi, 65–74.
27. PLUMMER, H. S.: Part 2. The function of the thyroid gland, *In:* MAYO, C. H., and PLUMMER, H. S.: The thyroid gland; The Beaumont Foundation Lectures, Series 4, 1926, C. V. Mosby Company, St. Louis.
28. JACKSON, C. M.: *In:* MORRIS' human anatomy, 1914, P. Blakiston's Son and Company, Philadelphia.
29. GRAY, H.: Anatomy, descriptive and surgical, 1908, Lea and Febiger, Philadelphia.
30. VIERORDT, K. H.: Anatomische, physiologische, und physikalische Daten und Tabellen, 1906, G. Fischer, Jena.

BROMIDE PSYCHOSES: DIAGNOSIS, TREATMENT AND PREVENTION *

By MAX LEVIN, M.D., *Harrisburg, Pennsylvania*

THAT psychoses may occur as a symptom of bromide intoxication has been known for many years, but only since 1925, when Hauptmann described a modification of Walter's [1] method for determining the concentration of bromides in the serum, has it been possible to diagnose them with ease. Before 1925 bromide psychoses doubtless were overlooked as frequently as syphilis in the days before the Wassermann test.

In spite of the help given by the Walter-Hauptmann test, the recognition of a bromide psychosis is not always a simple matter. The difficulty is very much like that sometimes encountered in cases of syphilis. A positive Wassermann reaction tells us that the patient has syphilis, but not whether the lump palpable in his abdomen is a gumma or some other kind of tumor. Similarly, when the Walter-Hauptmann test discloses a high [1] concentration of bromides in the serum, we know that the patient has a bromide intoxication, but from that alone we cannot tell whether his psychosis is due to bromides. The answer to this question depends on the following criteria.

1. We must know whether the psychosis began before or after the intoxication began. It is important not to confuse the bromide psychosis and the underlying neurosis or psychosis for which bromides were administered. Let us consider the example of a patient who begins to show the symptoms of a depression in January; in March he begins to take large daily doses of bromides, and in May he enters a delirium. If we now see him for the first time, and learn that he began to be psychotic two months before he began to get bromides, we might hastily exclude bromide psychosis from consideration. This would be a mistake, for in addition to the basic depression the patient now has a delirium that began *after* he became intoxicated.

2. We must consider the duration of the psychosis after the discontinuance of the bromides. Usually a bromide psychosis clears up within a

* Received for publication August 12, 1933.
From the Harrisburg State Hospital.

[1] The consensus of opinion is that a concentration of 150 or more milligrams of bromide per 100 cubic centimeters of serum warrants one in speaking of a bromide intoxication. Physicians must bear in mind two considerations: 1. It is possible that future research will show that some persons, abnormally susceptible, may develop bromide psychoses even before the concentration in the serum has reached 150 mg. 2. In evaluating the results of the bromide test one must consider the date of the test in relation to the date of discontinuance of the bromides. Suppose a man receives bromides until June 1, and I see him for the first time on June 28, at which time the bromide concentration is 75 mg. I would be greatly in error were I to conclude that, the bromide concentration being only 75, the patient's recent symptoms could not be the result of a bromide intoxication. A concentration of 75 *four weeks after discontinuance* would indicate that at the time of discontinuance the patient was loaded with bromides. Charts showing the rate at which the bromide concentration falls after discontinuance may be found in O. Wuth's [2] article.

short time—generally from two to six weeks—after discontinuance.* Here again we must be careful not to confuse the bromide psychosis and the underlying psychosis. In the hypothetical case cited above we will suppose that several weeks after discontinuance the delirium clears up, after which the patient continues for many months to show symptoms of depression. In this event it would be a mistake to argue that, discontinuance having led to no recovery, bromide psychosis may be excluded; correct diagnosis will be possible only if we recognize that the patient had *two* psychoses: (*a*) a depression, which began before the intoxication and now continues after the intoxication has subsided; and (*b*) a delirium, which began during, and cleared up simultaneously with, the intoxication.

If we bear in mind these considerations we shall rarely be misled by the Walter-Hauptmann test into diagnosing a bromide psychosis where none exists. To demonstrate their importance I have selected the following case, in which a bromide delirium occurred in a woman who had general paresis. The case is of special interest because of the well-known fact that bromide intoxication sometimes simulates general paresis.

Case Report

A woman of 42 was admitted to the Harrisburg State Hospital on June 29, 1932, in a delirium.

Present Illness. The sisters of the patient stated that one year before admission she began to complain of fatigue. It tired her, for example, to spend an hour or two downtown. In December 1931, her speech began to be affected; she stammered and halted, and her enunciation was not clear. At the end of May 1932, "her mind began to wander." *One week before admission disorientation was noticed for the first time.* While in her own bedroom she said, "I want to go home and be in my own bedroom." She saw imaginary babies in the room. During the week before admission she was so incoördinate as to be unable to walk.

Medication. The relatives stated that during the year before admission she was under the care of a physician, who gave her "nerve medicine" for an unbroken period of approximately six months, ending at the time of her admission.

Mental Examination. The patient was coöperative but very dull. There was marked difficulty in thinking of words. She was disoriented in all spheres. Her memory was poor.

Physical Examination. The patient was feeble and looked very old for her years. She was undernourished, her height being 5′ ½″ and her weight only 92 pounds. The pupils were of moderate size and irregular; the left was larger than the right; there was no reaction to light and only the barest reaction on accommodation. Speech was badly slurred. There was a coarse tremor of the tongue and fingers. Gait was slow and unsteady, and she was unable to stand with her feet together. The knee-jerks and ankle-jerks were hyperactive and equal. The physical examination otherwise showed nothing of importance.

Laboratory Examinations. The Walter-Hauptmann test on June 30, 1932, showed 350 milligrams of bromide per 100 c.c. of serum; July 13, 200 milligrams. The Wassermann reaction of the blood was negative. Spinal fluid: Wassermann reaction, plus 4; globulin, positive; cells, 3; mastic curve, 5555543000.

* There is no uniformity as to the level to which the serum bromide concentration must fall before a bromide psychosis clears up. In some cases a bromide psychosis clears up long before the concentration falls to 150 mg.; in others the concentration must first fall to 150 or less.

Course in Hospital. The patient emerged from her delirium on July 8—her tenth day in the Hospital. On that day she said, "I am beginning to be able to get my mind together and remember things. I don't jumble my words any more like I used to. Do you remember? Poor Mother never used to understand me; people had to tell her what I was trying to say. Now I speak plain." (Tell me more about the state of your mind at that time.) "I forgot everything. I'd start to say something and then I'd ask, 'What was I saying?' Mother was crying all the time—she was afraid I'd never get my speech back." (When you came here, did you know where you were?) "No. I asked the girls (nurses), 'Where am I? What is this place?' When they told me I was so near home, I couldn't believe it; I thought I was near Philadelphia." Throughout the remainder of her stay in the Hospital the patient was at all times clear and well oriented.

Neurological reëxamination on July 8 showed that the pupils now reacted moderately well on accommodation. They still showed no reaction to light. Speech was still slurred, but less so than on admission.

Following her recovery from the delirium the patient gained weight rapidly. Whereas on admission she had looked aged and worn out, she now began to look normally youthful, her facial expression being alert and animated. On September 2, 1932, she was inoculated with malaria. The first paroxysm occurred on September 10. Paroxysms occurred infrequently, the fifth and last occurring on September 27. Thereafter fever therapy was continued with the aid of injections of typhoid vaccine and hot packs. She continued to gain weight. She was paroled on December 10, 1932, weighing 116 pounds.

Catamnestic Note. On March 11, 1933, reëxamination gave the following results. She looked and felt well and was in excellent spirits. "I couldn't feel better." Memory, subjectively, was good. She retained seven digits. Calculation was not good. Thus, in subtracting successive 7's from 100, her performance during one minute was as follows: 93, *76, 89,* 82, 75, 68, 61, 54, *48.* The pupils were of moderate size, approximately equal, and irregular; they reacted moderately well on accommodation but were fixed to light. There was a moderate tremor of the face, tongue, and fingers. There was very slight slurring of speech; she had especial difficulty with "artillery." When asked to write "Methodist Episcopal," she wrote, in one word, "Methodistespespicopal," crossing the first "t" but not the second. The knee-jerks were hyperactive and equal. The ankle-jerks were active and equal. She swayed slightly when standing with feet together and eyes closed. Reëxamination on June 10, 1933, gave substantially the same results.

Comment

This case shows the importance of bearing in mind the mental disturbances arising from bromide intoxication. A physician unfamiliar with bromide intoxication might, on the patient's admission to the Hospital, have attributed all of her symptoms to general paresis. In view of the fact that she was then delirious, he might have concluded that her paresis was relatively advanced. In truth, she had paresis in a relatively early state. The symptoms that had caused her to be admitted to the Hospital were not those of paresis but of bromide delirium, the diagnosis of which is established by: (1) the disclosure of a severe bromide intoxication by the Walter-Hauptmann test; (2) the fact that the delirium had begun not more than one month before admission, and about five months after she had begun to take "nerve medicine"; (3) the clearing up of the delirium a short time (10 days) after the discontinuance of the bromides.

Attention is called to the absence of a rash in this case. Absence of a rash does not exclude bromide intoxication.

Attention is called also to the fact that at the height of the intoxication the pupils showed only the barest reaction on accommodation, while later they showed a moderately good reaction. This relative diminution of reactivity on admission may be ascribed to the intoxication.

I have already stated that bromide psychoses usually clear up in from two to six weeks after discontinuance. We may plausibly suppose that a patient with paresis would, if anything, require longer than the average to recover from a bromide delirium, and therefore the recovery of our patient in only 10 days may at first glance seem puzzling. We must, however, remember that different people possess different degrees of innate resistance to delirium. Conceivably a person may have such strong resistance to delirium that even when his resistance is lowered by paresis it still exceeds that of the average individual. In other words, the fact that our patient recovered sooner than the average is no more puzzling than the fact that *some* men at 60 can outwalk the average man of 30.

Varieties of Bromide Psychosis

Three varieties of bromide psychosis are known today: 1. *A state of mental sluggishness,* in which the patient thinks and acts with great difficulty, being at the same time well oriented and having no hallucinations. This state is commonly spoken of as a " simple bromide intoxication." 2. *Delirium,* in which the patient is disoriented, generally with restlessness, hallucinations, and a multitude of fears. (Disorientation is the one essential feature of delirium.) 3. *Hallucinosis,* in which the patient has hallucinations, but is perfectly oriented.

It is possible that additional varieties will become known as time proceeds. Thus, psychiatrists are familiar with paranoid states which clear up a few weeks after the patient's admission to a hospital. It is possible that some of these transitory paranoid states, when studied in relation to the criteria here outlined, will prove to be symptomatic of bromide intoxication.

In practically all cases of bromide intoxication neurological signs occur. The commonest of these are: irregularity of the pupils, and sluggishness in their reaction to light and on accommodation; tremors of face, tongue and fingers; thickness of speech; unsteadiness of gait and station; and diminution or exaggeration of the deep reflexes.

As a sample of the disorders on which bromide psychoses may be superimposed, the following data are cited. Among the 505 " first admissions " to the Harrisburg State Hospital during the two years beginning June 1, 1931, there were 15 unquestionable cases of bromide psychoses. Five of these patients had been given bromides because of a variety of neurotic symptoms, associated in some instances with abdominal, pelvic and other physical ailments; one because of herpes zoster; one because of worry over recently discovered hypertension; one because of an acute psychosis the

details of which are not clear; one because of a hypochondriacal depression developing on the basis of cerebral arteriosclerosis; one because of an excitement developing on the same basis; one because of early senile symptoms; one because of symptoms arising from general paresis (the case herein reported); one because of the after-effects of a concussion; and two because of epilepsy. Further details of eight of these cases may be found elsewhere.[3]

Treatment

An unsettled question is whether the abrupt discontinuance of bromides ever does harm. The aggravation of a few cases after discontinuance has led several authors to conclude that abrupt discontinuance is risky. In my earlier paper [3] I endeavored to show that the evidence so far available does not make this conclusion obligatory. The current practice at the Harrisburg State Hospital is to discontinue bromides, and so far nothing has occurred to cast doubt on the wisdom of this procedure.

The patient should be kept in bed until the intoxication has subsided. Fluids should be forced. If there is no nephritis, four grams (one dram) of sodium chloride should be given thrice daily, the chloride ion facilitating the excretion of the bromide ion. Restless patients should be given continuous baths. The need of using only the least toxic hypnotics is especially urgent in patients with bromide intoxication, poisoned as they already are; for the majority of patients who require hypnotics, paraldehyde will suffice. Cardiac stimulants should be given when indicated.

Prevention

Bromides are useful medicinal agents. What renders them so often harmful is that the busy physician too hastily dismisses his neurotic patient with the advice, "Keep on taking that salty medicine, the same as before." The patient, as a result, may be taking bromides for many months before the physician is fully aware of it. When the nervous symptoms grow worse, the physician is apt to increase the dosage of the bromides, without duly considering the possibility that the aggravation is due to bromide poisoning. It is important to remember that bromides will accumulate in the body in inverse proportion to the amount of chlorides ingested; a person who takes little table salt will therefore develop a bromide intoxication with especial ease. Moreover a patient may be getting bromides from several physicians simultaneously, and may thus develop an intoxication from a multiplicity of cautious dosages.

The following suggestions are urged:

1. When contemplating the administration of bromides, the physician should seek to ascertain whether the patient is already getting bromides from another source.

2. The physician should know whether the patient takes much or little table salt. In the latter case he should be doubly cautious.

3. The physician should not relax his vigilance just because the dosage he is giving is one that has proved harmless in the majority of his patients.

4. When a nervous patient getting bromides grows worse, the physician should promptly discontinue the drug unless he has good reason to believe that it bears no responsibility for the aggravation.

5. When a patient has been taking bromides for a month or more, it is wise to discontinue them occasionally for a week or two. An occasional Walter-Hauptmann test is the best way to make sure that the patient is not becoming intoxicated.

Summary

The following criteria establish the diagnosis of a bromide psychosis: 1. The existence of a bromide intoxication, as shown by the Walter-Hauptmann test. 2. The fact that the psychosis began after the patient had become intoxicated. 3. The fact that the psychosis clears up within a short time—generally from two to six weeks—after the discontinuance of bromides. (It is possible that in exceptional cases a bromide psychosis lasts much longer than six weeks after discontinuance.) It is important to differentiate a bromide psychosis from the underlying neurosis or psychosis on which it has been superimposed. An illustrative case is presented of bromide delirium superimposed on general paresis. The treatment and prevention of bromide intoxication are discussed.

REFERENCES

1. Katzenelbogen, S., and Goldsmith, H.: The hemato-encephalic barrier; diagnostic value of the bromide test in mental diseases, Am. Jr. Psychiat., 1931, x, 1045–1055.
2. Wuth, O.: Rational bromide treatment; new methods for its control, Jr. Am. Med. Assoc., 1927, lxxxviii, 2013–2017.
3. Levin, M.: Bromide delirium and other bromide psychoses, Am. Jr. Psychiat., 1933, xii. 1125–1163.

SUBACUTE BACTERIAL ENDOCARDITIS *

By J. H. Musser, M.D., F.A.C.P., *New Orleans, Louisiana*

The fact that I have seen in the Charity Hospital in New Orleans in the past two years many more cases of subacute bacterial endocarditis than I remember ever having seen in the past, has led me to review the history of 14 cases that I have observed in this period of time in order to present to you certain features of a disease which, in one section of the country at least, seems to be increasingly prevalent. Some years ago Blumer [1] wrote that "it is difficult to say whether the disease is actually increasing or whether there is merely an apparent increase due to increasing knowledge on the part of the profession to recognize the condition. Personal experience would rather favor the latter view." This may be true, but on the other hand it is rather doubtful that a sudden accession of knowledge should have come to the staff of the Charity Hospital in the last year, in which time as many cases of subacute bacterial endocarditis were recognized as in the previous 10 years. It was only a few decades ago that the disease was first recognized but since that time there have been innumerable communications in the medical press concerning it. Certainly as a result of the teachings of Osler, Janeway, Libman, Blumer and Lewis there is no excuse for any failure to recognize the condition because of lack of information. Libman says that "the disease is common"; Lewis notes the same; the late Frank Billings, according to Blumer, had seen over 100 cases. Among the British soldiers studied by Lewis and his associates, at the concentration point for heart cases in England, it was found that approximately 8 per cent of sick soldiers who developed heart disease and were invalided home, had subacute bacterial endocarditis. These observations point to the relative frequency of the disease if looked for and if borne in mind.

In reviewing these 14 cases that I have seen in the last two years I wish to say that with one exception all of these patients were observed in the Charity Hospital. I wish, furthermore, to indicate that the expressions of this type of endocarditis are often extremely indefinite and vague. The symptoms are so protean in character that the possibility of such a condition as subacute bacterial endocarditis existing in the individual who has not had previous heart valve damage is often not considered until ultimately certain signs and laboratory findings develop which make the diagnosis unmistakable.

Duration of Illness

Subacute bacterial endocarditis is separated from acute, bacterial, ulcerative or fulminating endocarditis by an arbitrary time period. Most phy-

* Read before the Montreal Meeting of the American College of Physicians, February 10, 1933.

From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and the Charity Hospital of Louisiana.

sicians consider bacterial endocarditis extending longer than a period of two months as being subacute, or over a year as being chronic. In this group of patients the course of the disease was variable, extending from a period of slightly over a month to somewhat over a year. The rather protracted illness that occurs so frequently will be exemplified by the following case report.

CASE I

J. P., a man of 32, was taken ill slightly more than eight months before his death. his illness coming on quite suddenly with chills, and fever which rose to 102°. He improved but was left with residual weakness and fatiguability. About a month after the onset he noticed that his heart occasionally skipped a beat. Gradually the patient went downhill and finally entered the hospital some six months before his death. At the time of admission to the hospital the most important physical observation was a rather harsh and loud systolic murmur heard over the mitral area and transmitted into the axilla. The pulmonic second sound did not seem to be accentuated and the heart was not enlarged. At the time of admission the leukocyte count was 7,700; the red blood cell count was 4,395,000; the blood culture was positive for *Streptococcus viridans*. The urine showed nothing of moment. Repeated blood counts showed very little alteration in the total number of red cells and the same thing held true for the leukocyte count. The spleen was enlarged and during the months he was in the hospital was definitely tender on deep palpation. He also developed during the course of the disease tender finger tips and ultimately clubbing of the fingers. Petechiae were present over the hands and feet. All the time the patient was in the hospital the temperature ranged from subnormal to 101°–102°.

At autopsy small hemorrhages were found in the internal organs; the mitral valve showed many small vegetations which were not friable; the valve itself was not fibrotic. There was also a vegetative mass 4.5 cm. in diameter on the endocardium of the left ventricle. Healed infarcts were found in the spleen. There was a focal glomerular nephritis with healed infarcts of the kidneys. A small subarachnoid hemorrhage was also noted.

Discussion. This patient was ill for many months before the ultimate lethal termination. In most of our cases the illness was not so protracted. In many of them the patient died within a few months after the apparent onset of the illness. Seventy-five per cent of patients are said to die between the third and eighth months and our figures are in accord with this observation of Blumer's. In one instance the patient died a little over a month after being admitted to the hospital but I have no definite information as to the exact time his illness began.

A definite history could be obtained from the other cases and the story invariably was that they had been sick not for days but for weeks. However, only one of the patients survived the first year after the onset of the infection.

The following case, which is briefly abstracted, illustrates the fact that the clinical picture may suggest that the infection causing death is some other than subacute bacterial endocarditis.

Case II

J. G., aged 19 years, had been ill, with evidence of rheumatic heart disease, for two months prior to admission. He had had one previous attack of rheumatic fever some seven years before admission to the hospital. Since then he had had several attacks of heart failure and his condition had shown a gradual downhill trend. When he was admitted to the hospital his chief complaints were increasing weakness and shortness of breath. The examination at that time showed a well nourished, anemic appearing boy whose heart showed a diffuse apical impulse, together with an apical thrill, systolic in time. The heart was enlarged to the left 11.5 cm. A murmur was heard in the mitral area, and in the aortic area a rumbling first sound with a soft blowing second sound. The spleen could not be felt and no petechiae were found. He had the usual vascular phenomenon of aortic insufficiency, including a blood pressure of 130 systolic and zero diastolic. The urine showed a few red cells on several examinations. He had a relatively marked anemia, the red cells being 2,925,000. The total white count was persistently between 13,000 and 15,000. He ran a septic temperature throughout the course of the disease; and the *Streptococcus viridans* was found in the blood after the fifth culture. The diagnosis was made of rheumatic aortic regurgitation, and subsequent subacute bacterial endocarditis. He died apparently from heart failure rather than as a result of an infectious process.

Discussion. In this instance the boy might well have had rheumatic heart disease in the acute phases were it not for the fact that his blood culture ultimately was found to be positive. He also gave a history of having had a petechial rash over his legs. Other interesting features of this case were: involvement of the aortic valves; the long delay before obtaining a positive blood culture, and the limitation of direct evidence of embolic phenomena to the occurrence of a few red cells in the urinary sediment on several examinations.

Blood Findings

There is a very general impression that the leukocyte count in subacute bacterial endocarditis is relatively high. Cotton,[2] of the Sobraow Military Hospital, in his considerable series of cases, found the average count to be 10,800. In the present series the count ranged from 4,000 to 65,000. Ten of the counts were under 11,000. In those patients in whom the count was frequently repeated there was a tendency for it to remain at approximately the same figure as the initial count. There were only two counts over 20,000; one of these was 65,000. Two counts fell between 11,000 and 20,000; one of 17,000, and one averaging around 14,000. The percentage of polymorphonuclears was in direct relationship to the increase in the total count. The counts showing practically normal figures also had a differential picture which was essentially normal.

Anemia is one of the characteristic features of the disease. In five of our patients the red count was under 3,000,000; in four it was under 4,000,000 and in four it was between 4,000,000 and 5,000,000. There were no extremes, such as the counts occasionally recorded in this disease, of less than 2,000,000 or over 5,000,000. The usual findings in our series may be illustrated by the following case.

Case III

E. H., aged 24, was admitted to the hospital on account of shortness of breath and cough. His illness started three months before admission with, in his words, "severe chest cough." Since then the cough had remained constantly present with more or less acute exacerbations. He had had no hemoptysis and no chest discomfort or pain. He entered the hospital January 11, 1932. No history could be elicited of any symptoms in the past even suggestive of rheumatism or the rheumatic state. The heart examination showed a systolic thrill over the apex of the heart. The heart border extended 2 cm. to the right of the sternum, and 13 cm. to the left. There was heard a low, long systolic murmur at the apex transmitted to the axilla. There was a questionable presystolic whiff which had a vague sort of crescendo character. The liver was enlarged; the spleen was palpable and the lungs showed basal râles. This man had fever of 102° on admission which was maintained between 99° and 101° with a pulse rate of between 110 and 128 during all the time he was in the hospital. The blood count on several examinations showed an anemia with a red cell count averaging 3,100,000, and a corresponding reduction in hemoglobin; the leukocyte counts were 8,000 or under and there was no change in the differential formula. On both occasions that a blood culture was made, *Streptococcus viridans* was isolated. A roentgenogram of the chest was taken because of the physical findings of a solidification which suggested an infarct. This was confirmed by the roentgenogram. The diagnosis was made of rheumatic heart disease with mitral stenosis on which was engrafted subacute bacterial endocarditis. This was confirmed at autopsy which showed a markedly enlarged heart; the mitral valve was affected. It was found to be stenosed and thickened, and on the surfaces was a collection of pinkish red polypoid vegetations. One leaf had been ulcerated. The left and middle aortic cusps were thickened with several small polypoid vegetations on their surfaces. The lungs showed definite areas of infarction, while the spleen, which was enlarged, did not show evidence of infarction nor was there any found elsewhere.

Bacteriology

In our series of cases of subacute bacterial endocarditis, streptococci were isolated from the blood stream in the majority of instances. Libman has pointed out that the only two organisms of moment as responsible agents are the green streptococcus in 95 per cent of the cases, and *Bacillus influenzae* in the remaining 5 per cent. In Blumer's series of cases streptococcus is reported 248 times; 169 times it is specified as the *S. viridans*. Pneumococci were found 16 times in this series; *B. influenzae* 16 times, and other organisms only exceptionally. In addition to the frequently found green streptococcus it is not unusual to find other organisms. For example, Lenhartz [3] found in a series of 37 cases one instance of *Staphylococcus aureus* and one of *Staphylococcus albus* endocarditis. Clawson [4] in an analysis of 220 cases found seven instances of *Staphylococcus aureus* infection as contrasted with 34 of streptococcal origin. Stich,[5] reporting on a case of subacute bacterial endocarditis due to *Staphylococcus albus*, states that next in order of frequency to the streptococcus comes *Staphylococcus aureus*, then pneumococcus and gonococcus and last of all *Staphylococcus albus*. There is apparently very little difference in the clinical expressions of the disease, when due to one or the other type of organism. Subacute bacterial endocarditis may in rare instances be produced by the meningococ-

cus. Gwyn [6] has reported on such a case. He states that there have been some few cases reported infected with this type of organism and gives references to seven such instances. Gwyn writes that there is "little deviation from the classic picture of subacute bacterial endocarditis." He advances as an explanation for the relatively large numbers of cases of chronic meningococcal septicemias that have been reported, the suggestion that they may represent an unrecognized meningococcal endocarditis. Recently Dickar [7] reported two cases of *Bacterium acidi lactici* endocarditis.

In the present series the positive blood cultures yielded only the *S. viridans*. In nine instances this organism was found by this procedure, in five cases the culture was negative though three of these five patients had definite bacterial endocarditis at autopsy. In the other two instances the organisms were not found and the patients did not come to autopsy but the clinical course of the disease was so characteristic that there could be little question of the diagnosis.

Considerable difficulty arises at times in growing the organism from the blood. In Case III just cited, that of E. H., organisms were isolated on two occasions in large numbers. In Case II, that of J. G., it was not until the fifth culture that a relatively profuse growth, 86 colonies per cubic centimeter of blood, was discoverable in the culture medium on the seventh day after withdrawal of blood. The difficulty at times in obtaining positive cultures is readily explicable because the green streptococcus is a slow grower, and the culture should be kept for at least 10 days before being discarded. It is advisable also to take considerable quantities of blood because frequently the counts may be as low as one to five organisms per cubic centimeter of blood.

TABLE I

Subacute Bacterial Endocarditis

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Cardiac murmurs	+	+	+	+	+	+	−	+	+	+	+	+	+	+	13
Anemia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
Enlarged spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	13
Petechiae	+	−	+	+	−	+	−	+	+	−	+	−	+	−	8
Tender or clubbed fingers	+	−	+	+	−	−	+	+	+	−	+	+	+	−	9
Other embolic phenomena	+	−	+	+	+	+	+	−	−	+	+	+	−	+	10
Blood culture	+	+	−	+	+	−	+	−	+	+	+	+	−	−	9
Leukocytosis	−	−	+	+	−	−	−	−	−	−	−	+	−	+	4
Hematuria	−	−	+	−	−	−	−	+	−	−	+	+	+	−	5
Previous arthritis	−	+	−	+	−	+	−	+	+	−	−	+	+	−	7

The case of A.B. represents the type of case in which the discovery of a positive culture of *Streptococcus viridans* makes possible the correct diagnosis in a patient with fever of undetermined origin.

CASE IV

A. B., a man of 50, was a big, strong, athletic type of individual. He was taken sick, about two months prior to the time he was first seen, with what was diagnosed as

grippe. Up until that time he had been absolutely well, in fact two months before he had had a most thorough physical examination, at which time his heart was judged to be entirely normal. Following this so-called attack of grippe he ran a slight degree of fever for many days. He felt miserable and wretched but was able to work about half of the time. Gradually the tiredness and weakness became so pronounced that he had to go to bed. Except for the fever, which was never very high, the physical examination revealed only a soft systolic murmur which was thought to be hemic. Several blood cultures were negative. In spite of the fact that he was gradually going downhill he showed nothing characteristic of any definite disease. After an interval of several months, he developed almost simultaneously tender finger tips and a positive blood culture. These two findings determined the diagnosis definitely. From this time on the tender finger tips occurred at intervals; petechiae were subsequently observed and the spleen once was the site of an infarction. The temperature, until the antemortem rise, was at no time over 101°. The leukocyte count remained persistently under 10,000.

Discussion. In this instance none of the characteristic features of bacterial endocarditis were present except fever of unexplained cause until the tips of the index and middle fingers of the right hand suddenly one day became quite painful and tender and remained so for several hours. Shortly after this the occurrence of a positive blood culture definitely showed that subacute bacterial endocarditis was present. As the disease progressed more typical symptoms developed.

Nephritis

Baehr,[8] among others, has stressed the importance of nephritis and other renal complications in subacute bacterial endocarditis due to anhemolytic streptococci. He has called attention to the occurrence of acute glomerular nephritis and of chronic glomerular nephritis in 91 cases of subacute bacterial endocarditis. Embolic glomerular lesions are found in many instances. An interesting group is constituted of those cases, only occasionally seen, in which there occurs an absence of streptococci from the blood stream together with the findings of a diffuse glomerulo-nephritis. It is in this group of patients that a true glomerular nephritis may be observed, whereas in the patients who have bacteria in the blood stream no evidence is found of diffuse glomerular nephritis. The suggestion has been made by Baehr that the glomerular damage may be the result of phenomena concerned in the recovery from infections.

In our series of cases there were five patients who showed red blood cells in the urine. These patients were individuals who had streptococci in the blood stream and it was assumed that the red cells represented embolic occurrences in the kidneys. This was confirmed in one of the postmortems in which definite renal infarcts were observed. In two instances there was evidence of definite nephritis: a focal glomerular nephritis in one case in which there were streptococci in the blood stream.

The abstracted history of one of the cases, that of J. P., already has been presented. He showed no definite evidence of nephritis while in the hospital except for an occasional granular cast. There was no fixation of spe-

cific gravity and for only a short time before his death was there any albumin in the urine. It is quite possible that the glomerular nephritis found at autopsy was one of long standing. A résumé of the history of P. D., the second case of nephritis, is as follows.

Case V

This patient, aged *27*, died one month after coming into the hospital. He had been perfectly well up to two years before his final illness but at that time he began to have arthritic symptoms such as pain and swelling of the elbows and knees. Six weeks before admission he caught a cold. The fever from which he was suffering, together with weakness and slight dyspnea on exertion, were the only subjective symptoms of moment aside from pain in the right ankle. The physical examination of this patient showed a heart which was slightly enlarged to the left. There was a diffuse, forceful, to and fro murmur in the aortic valve area. In the mitral area there was a systolic-diastolic murmur, and a presystolic thrill. The spleen was enlarged and hard. Repeated blood cultures were taken which were never positive. The urine had always a high specific gravity, quantities of albumin, occasional red cells and at one time the note was made that it was loaded with red cells. The leukocyte count varied between 3,000 and 8,000, polymorphonuclears being *73* per cent on an average. The blood chemistry was negative. The temperature in the hospital varied between subnormal and 101°, going over 100° only once; the pulse rate was never unduly rapid. At autopsy the heart muscle was found to be pale, flabby and with some dilatation of the left ventricle, which explained the slight cardiac enlargement. The aortic valves showed non-friable vegetations leading to marked disfiguration of the valves. A small vegetation was found on a leaflet of the mitral valve. The kidneys were enlarged, dark red in color with thickening of the cortical zone. Microscopically they showed marked changes in the glomeruli with dilatation of the loops of the glomeruli. The tubules were also swollen.

Discussion. The diagnosis in this case was in no way difficult. The patient had petechiae on his chest when he was first seen and subsequently had crops of them from time to time. His finger tips were clubbed; he had well marked anemia. The murmurs were thought to be due to a preëxisting rheumatic endocarditis but the autopsy findings indicated that it is quite possible that the lesion was entirely the result of the bacterial endocardial involvement. There was no question concerning the diagnosis of the existing nephritis, a nephritis which occurred in the patient who had, as Baehr noted, no streptococci in his blood stream after many cultures and who apparently was in the stage of recovery from the infection. His death was due to a combination of the heart and kidney condition rather than to the infection. During the last 10 days of the patient's life the temperature was never over 99°, yet he suffered from well marked cardiac failure.

Spleen

Enlargement of the spleen was an almost invariable finding; it occurred in 92 + per cent of the cases in this series. Six of these patients had definite infarctions in the spleen. As a matter of fact, infarction of the spleen seemed to be more common than any other embolic phenomenon except skin petechiae. The occurrence of splenic embolism and the characteristic pain that it produces are exemplified in the following case.

Case VI

D. P., a young colored woman, 19 years of age, came into the hospital November 22, 1931, complaining of pain in the left side of the abdomen and fever. The fever had been present for about three weeks. With it there was an occasional chill and the usual symptoms associated with fever. One week before she came into the hospital she had a sudden severe, sharp pain in the abdomen which has persisted. This pain was relieved by sitting up in bed. The pain and fever were the main symptoms. At the age of 14 this woman had arthritis which involved both knees and she has had recurrent attacks of tonsillitis. The important physical finding in the heart was a diffuse apex beat 9.5 cm. to the left of the midline; the right border of the heart was not enlarged. At the apex there was a soft systolic murmur which replaced entirely the first heart sound. The laboratory findings showed a red cell count of 3,900,000, and a total white count of 8,750 of which 78 per cent were polymorphonuclears. Blood cultures demonstrated a *Streptococcus viridans* infection. The temperature was occasionally up as high as 101° but the pulse rate was never unduly accentuated. The patient deserted and was re-admitted again February 14, 1932. In the interim the only occurrence of moment was a repetition of the severe, sharp, agonizing pain in the region of the spleen which came on during the bus ride to her home. On this admission the condition was worse than it had been. The systolic murmur had become much intensified, the spleen was further enlarged and the red cells had fallen to 2,400,000. This patient, several days after admission, suddenly developed a squint and ptosis of the left eye. Spinal puncture showed nothing. During a stay of several weeks in the hospital temperature was somewhat higher than on the previous admission. The patient again insisted on leaving.

Discussion. In this instance there is a clear-cut definite history and observations of the phenomena of embolic involvement of a splenic vessel. The pain as described in the above history was variable in its persistency as it usually has been in other cases. It may last only a few hours or again may persist for some days. Apparently the infarcts of longer duration must extend out to the periphery of the spleen and set up a definite perisplenitis. In several other instances there was evidence of involvement of the splenic capsule and in one case it was thought that a friction rub could be heard.

There is considerable variability in the size of the spleen. The splenic tumor of infection is not a greatly enlarged organ but can be definitely palpated, and is soft and painless. On the other hand, as shown by autopsy, in two instances the spleen was much more enlarged than would occur from simple infection alone. A sensation of hardness or induration on palpation was characteristic of the spleen, which was the site of infarcts.

Valves Involved

The occurrence of previous arthritis with endocarditis determines to a certain extent at least the location of the vegetative process of subacute endocarditis. In seven instances a clear-cut definite history was obtained of a previous rheumatic infection. In five instances there was no story which could remotely indicate a previous infection of rheumatic nature. In two cases it was believed there was congenital heart disease, because the valve apparently involved was the pulmonic.* The previous rheumatism in all

* At the present time there is a patient in the Charity Hospital with subacute bacterial endocarditis on a patent ductus arteriosus.

instances, except two, had caused injury chiefly to the mitral valve. In two instances the aortic valve was undoubtedly the one predominantly affected. It is a nice question as to whether or not the valvulitis of rheumatic fever is confined to one valve alone in most cases. Seven of our patients had evidence of both aortic and mitral disease. Of these seven, one was purely an aortic lesion with a minimal involvement of the mitral valve. In another instance the preëxisting valvular lesion was the typical mitral stenosis of rheumatic heart disease and the aortic lesion was questionable.

One of the interesting features of this disease is the fact that subacute bacterial endocarditis develops in an abnormal heart, and that the abnormality is either rheumatic valvular disease or some congenital defect. Very rarely indeed does it happen that valves, the seat of syphilitic disease, become secondarily infected with the green streptococcus; and the same may be said of the sclerotic valves of senescence. The occurrence of a superimposed bacterial endocarditis on syphilitic aortic endocarditis is so exceptional as to merit recording. Craven [9] reported such a case and in reviewing the literature found 11 further reports but discarded most of them as being based on evidence insufficient to substantiate the diagnosis.

The determination of the location of the primary infective lesion or the location of the most severe active endocarditis is difficult, in fact impossible. In three instances the mitral valve alone was affected and in these three instances the patient apparently had never had any previous heart damage. The evidence of mitral valve involvement consisted of a soft, blowing systolic mitral murmur without evidence of heart enlargement or of any of the findings of prolonged or chronic valvular heart disease.

That it is impossible dogmatically to state that such and such a valve is the chief one affected is proved by our autopsy experience. In one instance the vegetative processes involved only the auricular wall but in this patient no cardiac murmur was audible. Evidently healing had taken place after the valve was affected, if it was, and no evidence of infection could be demonstrated grossly. Incidentally mural endocarditis is relatively common. Particularly interesting in this connection is a case report in which we thought that engrafted upon a congenital heart lesion was a subacute bacterial endocarditis. Before reciting this case history it might be said we had one other case in which the findings were typical of congenital heart disease but which we were unable to prove at autopsy.

Case VII

O. C., a young white woman, 19 years of age, had been sick for three weeks prior to admission to the hospital. One month previously she had had a tooth extracted and a week later had fallen ill with high fever and chills. She was thought to have typhoid fever; the continued fever was the only symptom of note. She had had no other severe sickness in the past. We were unable to obtain any information at all suggestive of a congenital heart lesion.

The physical examination pointed distinctly to a low grade congenital pulmonic stenosis. Aside from the anemic, pasty appearance of the patient the only important

findings were in the heart, which showed a slight enlargement to the right. The first sound over the pulmonic area was distinctly accentuated. There was a loud, blowing diastolic murmur over this region and a softer, lower pitched systolic at the base of the heart, highly suggestive of congenital pulmonic stenosis. This patient rapidly went downhill and died some 10 days after admission to the hospital. During her stay in the hospital petechiae were observed on the buttocks. The spleen was found to be slightly enlarged and the leukocyte count ranged between 22,000 and 23,000; polymorphonuclears 80 per cent. The temperature was of the typical septic type. Four blood cultures were negative. At autopsy a slight enlargement of the spleen was noted and several small areas of infarction in the kidney (on one occasion red cells were found in the urine). Otherwise the chief findings were in the heart. The heart showed enlargement of the right ventricular wall which was approximately as thick as the left ventricular wall. The pulmonic cusps were thickened irregularly and narrowed. They were not fused and showed no vegetations. Two centimeters above the valve there was found a small vegetative growth measuring about 0.5 cm. in diameter and an interval of 1 cm. of normal artery separated a second vegetative area which was somewhat larger than the other, measuring about 1.5 cm. in diameter.

Discussion. This case was of unusual interest on account of several very interesting possibilities. Our original concept was that a bacterial endocarditis had been superimposed upon a preëxisting congenital heart lesion. This idea seems dubious in view of the fact that the valve cusps were thickened and irregular as if a chronic inflammatory process had involved them some time in the past. These autopsy findings would seem to discount the congenital origin of the lesion. Particularly to be emphasized is the fact that this girl, who was a school teacher, had had her heart examined more than once and had always been told it was normal. It seems more logical to assume that healing and reparative processes had covered and obliterated the vegetations on the valves but had not yet occurred in those situated higher up on the wall of the artery. Another possibility is that the girl might have had a bacterial endocarditis previously and that the final illness was a second attack as a result of the entrance of green streptococcus into the blood stream, the infection entering after the abscessed tooth was extracted.

Lewis and Grant [10] have reported on bicuspid aortic valves in infective endocarditis. They write that it is theoretically possible for normal valves to be converted into the bicuspid valves which are found at autopsy. Lewis states that "until we could deny that subacute infective endocarditis is a process capable of complete healing—and we are not yet in a position to enter upon such a denial—the possibility had to be borne in mind that certain instances of bicuspid valve, found apart from active endocarditis, might be the healed products of such an infection long since cured." Subacute endocarditis may have a long duration. It is rather difficult to conceive of the valve with its vegetations remaining unchanged over a long period of time. These vegetations may become scar tissue and represent commissures, ulcerated and subsequently healed and retracted. In view of these statements of Lewis', might it not be presumed that in this particular instance the pulmonic valve had been involved months previously and the endocardial lesion

had become quiescent, either completely cured or else remaining as a small locus on the artery to become reactivated under the influence of infection at the time the tooth abscess existed.

Here it might be appropriate to comment on subacute bacterial endocarditis occurring after tooth extraction. A review of the literature of the last several years shows a general recognition of the fact that the possible appearance of subacute bacterial endocarditis after the extraction of a tooth or of teeth is a definite hazard to be feared. Bernstein [11] reports the development of a fatal subacute endocarditis in a young man within five days following the extraction of a tooth. Brown [12] reports another such case. Recently, within the last six weeks, I have seen in consultation an old gentleman dying from an acute endocarditis, the symptoms of which came on about one week following the extraction of half a dozen infected teeth. The disease may follow other operative procedures on streptococcic foci. Abrahamson [13] reports a case of subacute bacterial endocarditis following the removal of tonsils, as well as two others in which it followed the extraction of teeth. This author stresses the fact that evidence such as this would tend to prove that the organisms of subacute bacterial endocarditis may come from the teeth or tonsils. Under any circumstance, the many reported occurrences of the disease after measures to remove foci of infection indicate that extreme precautions should be taken when such foci are eradicated by surgical procedures in patients with preëxisting valvular disease.

According to Lewis not only are there instances of recovery from subacute bacterial endocarditis but it is remarkable in some cases how little effect its presence may exert upon the heart. In this conjunction it is of interest to note the report of a case of a woman who died suddenly as a result of involvement of the right and left coronary arteries by vegetations which obstructed the blood supply to the heart. In this instance the patient had apparently been entirely well up to the time of her sudden death and was not even cognizant of the fact that her heart was affected or that she had had a recent infection.[14] In discussing atypical initial symptoms Mallory [15] mentions cases presenting the clinical symptoms and signs of Raynaud's disease, and others having appendectomy performed for what turned out to be an intestinal embolus.

Embolic Phenomena

The most definite, positive, substantiative finding is the occurrence of embolic phenomena. I have already noted the occurrence in this series of red cells in the urine in five instances, indicating the presence of renal emboli. Outstanding embolic symptoms occurred in five instances in the spleen. In one case, D. P., already mentioned in detail, the occurrence of squint and ptosis of the eye indicated cerebral embolus. A subarachnoid hemorrhage was found at autopsy in the case of J. P. Five of our cases showed very definite tender fingers, the nodes of Osler, transient painful areas of redness in the finger pads. None of them exhibited splinter hemorrhage under the

finger nails as described by Blumer. Retinal hemorrhages or subconjunctival hemorrhages were never seen. In eight instances petechiae were definitely observed on different parts of the body. In two instances gross vascular lesions occurred which were quite spectacular. In one instance, a boy, in fairly good condition despite the bacterial endocarditis, had a sudden hemorrhage from the mouth and promptly died as a result of the blood loss. In this instance the bleeding was probably due to an embolic or mycotic aneurysm although no evidence that such existed was discoverable before his death. Unfortunately there was no autopsy. This boy was the youngest of our group of patients, being only 13 years of age.

Case VIII

The most spectacular case of vascular occlusion occurred in the instance of C. H., the oldest of our group, a white male aged 57. He was in the hospital for two and a half months. His chief complaint was weakness and shortness of breath, both of which had been gradually progressing for a period of two years although he was not advised to stop work until shortly before admission to the hospital. He came into the hospital because of acute, severe pain in the upper part of the abdomen. The physical examination showed a man considerably emaciated. He was extremely dyspneic and had other significant findings of congestive failure. The heart border was 12 cm. to the left of the midsternal line and the sounds were poor in quality and rapid. No murmurs were audible. The radial arteries showed no signs of gross arteriosclerosis. The spleen was decidedly enlarged and very tender. The patient ran a septic temperature during his stay in the hospital. Three days before his death he had severe pain in his arms with disappearance of the radial pulse on both sides, a quite remarkable coincidence. The fingers of the left hand and thumb of the right hand rapidly became bluish-black in color and gangrene set in. Laboratory examinations were as follows: the urine showed no red cells; the hemoglobin was 50 per cent; red cells 2,500,000; leukocytes 4,500, 69 of which were polymorphonuclears. At the autopsy two days later emboli were found in both of the radial arteries. There were vegetations (2×4 cm.) amidst the papillary muscles of the left auricular wall. Polypoid vegetations were found on the mitral valve and on the aortic valve. The spleen showed evidence of numerous infarcts as did the kidneys.

Discussion. This patient was apparently dying of congestive heart failure. The immediate cause of death, or better the actual accident that terminated the life of a man already near death was the occurrence of the emboli in the arms and in the spleen. This cardiovascular accident was just enough to be fatal.

Evidences of involvement of the lung by emboli were found twice at autopsy. In one instance, that of E. H., already quoted, the lungs showed rather extensive evidence of infarction but no evidence of emboli causing hemorrhagic infarcts were found elsewhere in the body; a rather interesting observation in view of the fact that the right heart was entirely normal and that such pulmonary emboli must have come from some unrecognized area of thrombosis of a peripheral vein. In the instance of O. C., right endocardial involvement was found but there were no areas of infarction other than those in the spleen and kidneys.

Summary

The clinical data of a group of patients who died from subacute bacterial endocarditis are reviewed. For the most part this group adhered ultimately to the more or less classical, clinical features of this disease. Eleven of them were under 30 years of age; seven definitely had had a previous arthritis of rheumatic origin. Nine of them had positive blood cultures. All of them had anemia of various grades and all of them showed embolic phenomena of various types. One rather odd feature is that in one instance no murmurs were heard despite repeated efforts to observe these particular physical signs.

Conclusions

In this present series of cases it is true that ultimately and eventually the correct diagnosis was obtained but it was obvious that often the diagnosis may be in abeyance for weeks before definite clinical phenomena are exhibited which will determine positively the presence of subacute bacterial endocarditis in patients sick with fever over a long period of time. No conclusion can be drawn as to the apparent increase in the occurrence of this disease other than it is reasonable to suppose that the disease is more frequent than it used to be.

REFERENCES

1. Blumer, G.: Subacute bacterial endocarditis, Medicine, 1923, ii, 105–170.
2. Cotton, T. F.: Observations on subacute infective endocarditis, Brit. Med. Jr., 1920, ii, 851–854.
3. Lenhartz, H.: Über die septische Endocarditis, München. med. Wchnschr., 1901, xlviii, 1178–1180.
4. Clawson, B. J.: Endocarditis, with special reference to subacute bacterial type, Arch. Int. Med., 1924, xxxiii, 157–184.
5. Stich, B.: Subacute bacterial endocarditis due to *Staphylococcus albus;* report of case, Arch. Int. Med., 1932, xlix, 666–670.
6. Gwyn, N. B.: Subacute meningococcal endocarditis, Arch. Int. Med., 1931, xlviii, 1110–1117.
7. Dickar, L.: Acute bacterial endocarditis due to *Bacterium acidi lactici,* Arch. Int. Med., 1932, xlix, 788–798.
8. Baehr, G.: Renal complications of endocarditis, Tr. Assoc. Am. Phys., 1931, xlvi, 87–95.
9. Craven, E. B., Jr.: Syphilitic aortic endocarditis and superimposed bacterial (*Streptococcus viridans*) endocarditis, Am. Jr. Path., 1932, viii, 81–90.
10. Lewis, T., and Grant, R. T.: Observations relating to subacute infective endocarditis; note on normal structure of aortic valve; bicuspid aortic valves of congenital origin; bicuspid aortic valves in subacute infective endocarditis, Heart, 1923, x, 21–99.
11. Bernstein, M.: Subacute bacterial endocarditis following extraction of teeth; report of case, Ann. Int. Med., 1932, v, 1138–1144.
12. Brown, H. H.: Tooth extraction and chronic infective endocarditis, Brit. Med. Jr., 1932, i, 796–797.
13. Abrahamson, L.: Subacute bacterial endocarditis following removal of septic foci, Brit. Med. Jr., 1931, ii, 8–9.
14. West, G. L.: Sudden death in case of asymptomatic subacute bacterial endocarditis, New Eng. Jr. Med., 1931, ccv, 675–678.
15. Mallory, T. B.: Aortic regurgitation beginning at the age of fifty years in a man who suffered from attacks of unexplained fever, New Eng. Jr. Med., 1932, ccvi, 1214–1217.

THE RÔLE OF DESENSITIZATION IN RECOVERY FROM BACTERIAL INFECTION *

By W. B. Wherry, *Cincinnati, Ohio*

Our conception of what goes on during infection and recovery is bound to undergo a change from time to time, for our knowledge of biological processes is always incomplete and we are being perpetually subjected to the influence of new discoveries. The hypothesis I am going to present to you when carried to its logical conclusion is not clear in all its details, but it has directed us in our experimental work and has brought forth results which will aid us in combatting bacterial infections.

An important factor in susceptibility and immunity, and one that largely has been overlooked, is that it is requisite in order for bacteria to thrive and multiply that they have food in solution. Since there is little or no free water in the colloids of normal tissue cells, bacteria must be able to put the colloids into solution—either through direct ferment action or by producing substances which are capable of hydrating colloids, or substances which when split by body ferments will yield tissue hydrating substances. In all probability some of these substances are amines. Since the known "soluble toxins" of bacteria require an incubation period after injection before their toxic action is manifested, it seems probable that the real toxin is not present in what we have been calling toxin but is liberated when a pretoxin is digested by body ferments. If an animal is possessed of ferments capable of splitting off toxic material from a pretoxin, that animal is susceptible; if an animal possesses ferments which are unable to digest a pretoxin, or if the split products are non-toxic, that animal is immune. Other factors are important in determining the relationship between parasite and host but I believe the factors concerned in tissue hydration deserve more consideration than they have received in the past.

Presenting the thesis in a different way—a microörganism can lead a parasitic existence only if it is provided with ferments which can act on the food substances provided by a host; if it can thrive at the low oxygen tension found in living tissues; if it can put the gels of the host into solution. If after implanting itself in the tissues of a host the interaction between the parasite and the host leads to the liberation of substances which injure the host and interfere with the normal defense mechanism of the host, then the parasite is a pathogenic parasite. Tissue hydration is detrimental to the normal defense mechanism because the local edema dilutes the antibodies, immobilizes the phagocytes and furnishes food in solution for the bacteria. While it is true that toxic substances may be localized for a time at the site of reaction, this results in many instances in local necrosis of fixed tissue cells. Other evidence that edema is an extremely important factor in in-

* Read at the Montreal Meeting of the American College of Physicians February 6, 1933.

fection is shown by the fact that if at the beginning of an infection the tissues are strongly dehydrated the infectious process is brought to an end.

Tissue hydrating substances are produced by bacterial ferments from suitable media. They may be liberated by autolysis of bacteria, or through the action of body ferments upon the bacterial protoplasm or products. It is through the action of such toxins that the phenomena of inflammation are produced.

In the sensitized animal the ability to split a specific protein is greatly enhanced and the phenomena of ordinary inflammation are greatly exaggerated and altered in certain directions. Here the reaction between parasite and host leads to very marked local edema. In many infections, tuberculosis, glanders, diphtheria, scarlatina, undulant fever, tularemia, one can demonstrate easily that the host is acutely sensitized by injecting a minute quantity of the specific antigen intradermally. I believe that further investigations will reveal the fact that in every case of infection the host is either already sensitized or becomes sensitized soon after infection. Some infections are uniformly accompanied by marked hypersensitivity, e.g. glanders, tuberculosis, undulant fever, tularemia. In a disease like tularemia of the ulcero-glandular type, where it is possible to determine the exact time when a patient lacerated his finger with the broken bone of a rabbit, and therefore just when infection occurred, Lee Foshay [1] has found that the patient is acutely sensitized at least as early as the third day after infection.

The degree of hypersensitivity manifested by different hosts infected with the same germ may vary considerably. In cases infected with *Staphylococcus pyogenes* one may encounter skin reactions of moderate degree or of very violent degree (marked congestion and edema, chills and fever, adenitis, local necrosis of skin).

When a sensitized animal is reinfected with the microörganism which produced the sensitivity this superinfection runs a course modified by the phenomena of anaphylaxis. Many of the objective manifestations of infectious diseases occur only after superinfection. In his work on the production of yaws in monkeys Otto Schöbl [2] was able to produce some of the later clinical manifestations, as seen in man, only when he practiced superinfection in sensitized animals.

There is an increasing amount of evidence to show that hypersensitivity to foreign proteins other than bacterial—pollens, foods, emanations, etc.—may favor infection. Shock to one bacterial protein may lower resistance by creating conditions which favor invasion by another species. Bull and McKee,[3] during their studies on spontaneous respiratory infections in rabbits, made the following interesting observation: rabbits recovered from pneumococcus infection were found to be hypersensitive. Such rabbits were made " carriers " of *B. leptisepticum*. Now when a homologous pneumococcus autolysate was instilled into the rabbit's nostrils they developed local anaphylactic shock and this was followed in a few hours by an infection

with *B. leptisepticum*. This train of events can be applied to explain what happens frequently in many affections of the respiratory tract.

Now, from the moment when hypersensitivity is established the host is handicapped in the contest with the invader and the very best aid we can give must concern itself with measures which will remove this state of hypersensitivity. This can be accomplished by active and passive desensitization. I became convinced several years ago that the best way to discover the offending bacteria in mixed infections was to isolate them, kill them by heat, and make intradermal tests. A few other workers have made a practice of this procedure.[4, 5, 6] I have pointed out the usefulness of this method in determining the rôle played by a large variety of bacteria when their proteins are absorbed through an abnormal mucosa, e.g. in cases of acute and chronic sinusitis, colds, bronchial asthma, urticaria, angioneurotic edema, chronic arthritis and spastic and mucous colitis; and have shown that when suitably prepared antigens are used for desensitization such patients may be desensitized and that desensitization is accompanied by recovery.

Active desensitization has been brought about successfully by administering small doses of specific antigen, subcutaneously, at short intervals. This is essentially the method of Besredka. Where the hypersensitivity is marked we have found it necessary to detoxify the antigen and have obtained the best results by the use of reducing and oxidizing agents—formaldehyde, hydrogen peroxide, and nitrous acid. G. E. Rockwell[7] has applied this method to the detoxification of rag weed pollen and successfully immunized a few cases of hay fever during the past season. Such active desensitization is of practical use only in subacute and chronic infections for it usually requires from several weeks to several months, depending upon the degree of hypersensitivity, to bring about the desired result.

In many instances the host, although apparently recovered from an active infection, still suffers from the sequellae which are associated with a persistent hypersensitivity. Such sequellae are best treated by desensitization. I treated a case of sciatica which had persisted for a year after convalescence from Malta fever by practicing desensitization. Just as soon as slight tolerance to the antigen was established the pain disappeared.

Lee Foshay[8] has found this to be true in tularemia. In this disease convalescence is very prolonged. Although the patients have recovered from the active infection, and the pus from suppurating glands no longer harbors viable *B. tularense,* the patients are not well. They do not feel well. Their swollen glands liquefy and discharge pus for many weeks. While vaccinating such a case Foshay noted that just at the point where increased tolerance to the antigen was established, the edema of the glands disappeared and they shrank to normal size in a few days.

For the treatment of acute bacterial infections accompanied by hypersensitivity our hope must lie in the production of desensitizing antisera. This was accomplished two years ago by Foshay[8] when he produced a serum which will cure tularemia in man. Goats, immunized by subcutaneous ad-

ministration of small, often repeated doses of formaldehyde treated antigen over a period of four months or longer, yield a serum which will not protect the highly susceptible guinea pig or rabbit against infection, but will desensitize and cure a human case within four days. One accomplishes here in a few days by *passive desensitization* that which can be brought about only by several months of active immunization. Up to date Foshay has treated 64 cases of tularemia with results which have passed all expectations. As little as 5 to 7 c.c. of serum has been sufficient to cure a case. Indeed one of the striking features of antisera prepared in this way has been the remarkable effectiveness of small doses of unconcentrated serum in reducing fever, and in causing the disappearance of visible anaphylactic phenomena.

Sera prepared by immunizing goats with detoxified antigens have been prepared against *B. abortus*, and streptococci (hemolyticus, viridans, fecalis). We consider these latter sera to be in the experimental stage.

Details concerning the serum treatment of 60 cases of tularemia have been presented by Foshay.[9] A preliminary note on the serum treatment of four cases of undulant fever has been published by O'Neil.[10]

BIBLIOGRAPHY

1. Foshay, L.: Tularemia; accurate and earlier diagnosis by means of intradermal reaction, Jr. Infect. Dis., 1932, li, 286–291.
2. Schöbl, O.: Experimental yaws in Philippine monkeys and critical consideration of our knowledge concerning framboesia tropica in light of recent experimental evidence, Philippine Jr. Sci., 1928, xxxv, 209–332.
3. Bull, C. G., and McKee, C. M.: Sensitization of rabbits to products of pneumococcus resulting from acute infection with this organism, Am. Jr. Hyg., 1929, ix, 666–681.
4. Wherry, W. B.: Tissue hydration and its relation to susceptibility and immunity as shown by skin tests in asthma, chronic sinusitis and other infections, Jr. Infect. Dis., 1927, xli, 177–189.
5. Wherry, W. B.: Hypersensitivity to bacterial proteins and its rôle in susceptibility and immunity, Am. Jr. Hyg., 1931, xiv, 539–554.
6. Dorst, S. E., and Hopphan, E.: Angioneurotic edema: its relation to bacterial hypersensitivity, Jr. Lab. and Clin. Med., 1932, xviii, 7–11.
7. Rockwell, G. E.: The detoxification of pollen antigens, Jr. Bact., 1933, xxv, 100.
8. Foshay, L.: Serum treatment of tularemia, Jr. Am. Med. Assoc., 1932, xcviii, 552.
9. Foshay, L.: Jr. Am. Med. Assoc. (In press.)
10. O'Neil, A. E.: Preliminary note on the treatment of undulant fever in man with detoxified vaccine and with antiserum, Ohio State Med. Jr., 1933, xxix, 438–439.

THE FAMILIAL INCIDENCE OF PEPTIC ULCER *

By HERMAN H. RIECKER, M.D., F.A.C.P., *Ann Arbor, Michigan*

CLINICIANS have taught for a number of years that gastric and duodenal ulcers occasionally occur in more than one member of a family, but the fact never has received recognition in the American literature, nor is it generally considered in discussions concerning the etiology of the disease. Stewart's [1] recent studies indicate that about 10 per cent of the population have ulcer at one time or another, and that while only about 5 per cent of ulcers become cancerous, in his series 16.8 per cent of gastric cancers arose in simple ulcers. Considering these figures, the familial incidence of the disease becomes of importance from the standpoint of the diagnosis and of the control of both conditions.

In 1897, Dreschfeld [2] noted the presence of ulcer in six families. In two instances, mother and daughter suffered with it; in one, father and daughter; in two, two sisters; and in one, a brother and sister. In 1907, Huber [3] described 30 instances and from his experience gave the incidence of familial ulcer as 15 per cent. In these 30 families there were 80 cases of ulcer, and 10 of cancer of the stomach. In 1910, Czernecki [4] published the history of a family in which a mother, son, and three daughters had peptic ulcer. Plaut,[5] in 1913, found a family history of ulcer in 22 per cent of 50 cases of ulcer. Verbrycke,[6] in 1915, reported two families, in one of which the mother, two sons and a daughter had peptic ulcer, the children's cases being confirmed by operation, while in the second family the mother died of cancer of the stomach and a daughter had ulcer. A case of ulcer was recorded by von Plitek,[7] in 1914, in which a history was given of a brother and two cousins who had been operated upon for ulcer.

Spiegel's [8] paper, published in 1918, contained a complete survey of 121 cases of peptic ulcer compared with 200 control cases distributed as follows:

	Family History of Ulcer	Family History of Cancer of Stomach
Ulcer patients 121	26.4%	14.8%
Control cases 200	5.5%	2.5%

A. F. Hurst,[9] in 1921, drew special attention to the subject by describing six families in which ulcer had occurred in more than one member. In reviewing the literature at this time he quoted Strauss [10] as having stated that in patients having ulcer, a family history of gastric disorder was obtained in one-third of the cases, while in non-gastric conditions such a history could be obtained in only one-twentieth of the cases.

In 1913, Dauwe [11] reported eight cases of ulcer with a family history of

* Received for publication December 23, 1932.
From the Department of Internal Medicine, University of Michigan.

the same condition. The incidence of ulcer was distributed among these patients' relatives as follows: the father had ulcer in four instances; the mother in four instances; a brother twice. Two relatives were affected in two of the cases. Dauwe believed the ulcer tendency to be inherited chiefly from the mother, and that a neurotrophic theory best explained the mechanism. This theory has been expounded by Mathieu and Moutier [12] and more recently by Draper.[13] Dauwe insisted that the neurogenic factor was primary in the causation of ulcer and that gastric hypersecretion was a secondary effect, a theory to which Bloomfield [14] emphatically subscribes.

In 1925, Huddy [15] reported two families, in one of which the mother and four sons had peptic ulcer, while in the other the mother had a cancer which had developed from an earlier ulcer, and her son had a duodenal ulcer. These cases were proved by operation. Wilkie,[16] in 1927, stated "There would appear to be an undoubted hereditary tendency to ulcer, particularly in females. I have had to deal with two families in each of which three sisters had to be operated on for duodenal ulcer."

Menasci,[17] in 1930, described the histories of two brothers, 39 and 31 years of age, both having ulcers in the prepyloric region. The father of these patients had died of carcinoma of the stomach, an uncle had died of perforated ulcer, an aunt had been operated on for ulcer, and another aunt had stomach trouble and nervousness. Menasci reviewed 71 cases of ulcer, 51 in men and 20 in women. There were 12 cases of cancer of the stomach in the families of these patients and an incidence of familial gastric disease (probably ulcer) of 26.7 per cent. He quoted Polacco who found an incidence of cancer of the stomach in ulcer families of 19.7 per cent. Menasci's results are in contrast to those of Ruhmann [18] who found a history of familial gastric disease in 48 per cent of 50 ulcer cases, and of Grote who found evidence in 60 per cent. They compare well with the figures of Britt,[19] which are 25 per cent; of Plaut,[5] 22 per cent; and Zisa,[20] 33.3 per cent.

In 1923, Aschner [21] reviewed the subject, incorporating Spiegel's cases, and adding 132 cases of her own with 200 controls, with the following results:

	Family History of Ulcer	Family History of Cancer of Stomach
132 ulcer cases	12.7%	9 %
200 control cases	4.5%	1.5%

I have reviewed the clinical charts of 942 duodenal ulcer cases, diagnosed at the University Hospital over a period of five years. All charts were accepted which contained a family history, and about which there was no reasonable doubt as to the correct diagnosis. Confirmation by roentgen-rays had usually been obtained. In such a review, I was obliged to accept the family histories as such, and the proportion of cases giving a positive family history of ulcer is lessened considerably by fragmentary or inaccurate information. However, many of the histories were taken by senior medical

students and were quite detailed. All of them were checked by a member of the staff, and in probably none was the questioner consciously attempting to elicit a history of ulcer. There was exhibited considerable keenness to find evidence of cancer in the family, and I attributed this to the influence of the teaching of the late Aldred Scott Warthin [24] whose opinions concerning this subject are well known.

A history of "symptoms similar to my own" by the patient was considered sufficient evidence of ulcer to be included, because duodenal ulcer gives a constant and rather striking history not easily confused with functional disease. The greatest sources of error in this study lay in the fact that many patients have no clear memories of family illnesses, that the number of living adults among the siblings could not be taken into consideration, and that many times a part of the family history was noted simply as "negative." All such histories had to be included in the total number because any selection would favor a higher percentage of ulcer families.

The data are compiled under two headings: (1) a history of ulcer in parent or sibling of the patient, and (2) a history of cancer of the stomach in either.

TABLE I

Distribution of Ulcer and Cancer in the Families of 121 Cases of Duodenal Ulcer as Recorded in the Histories

Grandfather		Grandmother		Father		Mother		Brother		Sister		Uncle		Aunt		Total	
U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca
2	2	0	1	30	20	14	4	50	1	15	1	3	6	1	1	115	36

Ulcer—U.
Cancer—Ca.

DISCUSSION

In the series of 942 cases of duodenal ulcer there was a family incidence of ulcer or cancer, or both, in 124 cases, or 13.0 per cent. The diagnosis was indeterminate in three cases and these were omitted in a study of the distribution among the relatives, as shown in table 1. A history of cancer of the stomach in a relative was obtained in 2.0 per cent which is not far from the general incidence as given by Stewart and Spiegel. However, in 121 cases of duodenal ulcer there was a family history of carcinoma of the stomach in 36 cases.

All cases of peptic ulcer are not of a familial nature, but from this study it would seem that in those with a positive family history at least one-third of the families will show a death from carcinoma of the stomach. This phase of the subject was studied by Ernst Spiegel in 1918 who found a positive family history of stomach disease in 74 of 121 cases of peptic ulcer. In these 74 cases, carcinoma of the stomach occurred in 18, or about one-fourth of the families.

Both Spiegel [8] and Bauer [22] think that ulcer is four times more common

in the families of ulcer patients than in those of the controls, and that cancer of the stomach is six times more prevalent in the ulcer families.

The problem could be approached by finding the frequency with which ulcers occur in the families of cancer patients. In a series of 31 such cases I found three families in which ulcer occurred, giving about the same percentage incidence as was obtained by studying the ulcer cases alone.

The results may be discussed with regard to the viewpoints that (1) cancer is inheritable as an organ-predisposition tendency, and (2) that cancer is engrafted on the site of ulcer in the stomach. This study could be interpreted in favor of the view that it is the tendency to ulcer which is carried in the family strain, and that the organ predisposition to cancer is on the basis of the occasional tendency of gastric ulcer to become cancerous. Any other interpretation would fail to explain the intermingling of the two diseases in the same family. A thorough study of the family history in cases of cancer proved to be engrafted on an ulcer might be of value in this connection.

An interesting example of the relation of ulcer to cancer in the same family is the following: In 1925, a man, aged 54, having been unsuccessfully treated by medical measures for a large gastric ulcer which had been present for six years, was referred for operation. Dr. Hugh Cabot found a large ulcer on the posterior wall of the stomach and, after removing a piece for pathological study, was obliged to cauterize it on account of its position. The pathological diagnosis was cancer on an ulcer base and the patient died two years later. In 1932, a younger brother of the above patient, aged 47, came to the hospital giving a typical history of duodenal ulcer, the diagnosis being confirmed by roentgen-ray.

A multiple incidence of ulcer in the family occurred 16 times in my series. The following case is an example of this tendency. A man, aged 29, entered the hospital in 1921 where a gastroenterostomy was done for duodenal ulcer. After numerous recurrences he was admitted again in 1931, when the following data were obtained: The patient's father had peptic ulcer, a brother had died of it at the age of 49, one other brother and two sisters of the six siblings have peptic ulcer, making six cases in this family in the two generations. The father was of English, and the mother of French-Canadian descent. The father was "nervous," the mother an epileptic, and the patient had several stigmata of psychoneurosis.

This study confirms the general impression that peptic ulcer commonly occurs in families, but so do other non-allergic diseases, such as gall-stones, rheumatic fever, cancer, and diabetes. We do not know the etiology of ulcer but, as in other diseases, the familial occurrence offers an unexcelled opportunity to study comprehensively such factors as the environment, food habits, constitutional type, and psychological pattern of the patients, all of which have been suggested as of etiological importance.

The inheritance of ulcer from the mother as emphasized by Dauwe was not prominent in this series, since there were only 10 ulcer cases in women.

In my series there was a father-son incidence in 47 cases, a mother-daughter relation in two cases, a mother-son relation in 15 cases, and father-daughter relation in 3 cases. However, in the cases reviewed from the literature, Dauwe's observation is, at least, partially substantiated, particularly by the reports of Huber and of Huddy.

The low percentage for the familial incidence of ulcer in this series is difficult to explain on any other basis than that the examiner was conservative in, or careless regarding, the importance of the family history. The incidence in a carefully worked out series should approach 30 per cent of the total cases on the basis of the data found in the literature, and of my personal experience with the disease.

Bauer and Aschner [23] have discussed at length the possible constitutional factors involved in the inheritance of ulcer and conclude that there is a recessive predisposition to the disease. They are in disagreement with Zisa [20] and Czernecki,[4] who believe there is a very distinct constitutional type, the asthenic build, which predisposes to ulcer and which in turn is, of course, inherited. Bauer and Aschner could find no distinct type of body build characteristic of their cases.

If we accept the opinion of Zisa that the asthenic constitution is particularly predisposed to ulcer, and consider also the frequent coincidence of ulcer and hysteria, we may put forward the hypothesis that it is in those families in which asthenic builds and neurotic traits are common that a high incidence of ulcer will be found. In my series there was a clear example of such a family; the grandmother, mother, aunt, and daughter, all were of an asthenic build and highly neurotic. Each had a definite history of ulcer. The daughter and the mother are our patients, and the aunt is a patient in a nearby hospital.

Conclusions

In 942 duodenal ulcer cases there was a family history of ulcer in 13.0 per cent. In 121 cases having a positive family history, the familial incidence of carcinoma of the stomach was 33 per cent.

There is a familial incidence of peptic ulcer in upwards of 30 per cent of the cases reported in the literature, which strongly supports the constitutional viewpoint of the etiology of the disease.

The incidence of carcinoma of the stomach in families with a history of ulcer is considerable higher than in the general population.

BIBLIOGRAPHY

1. Stewart, M. J.: Precancerous lesions of alimentary tract (Croonian lecture), Lancet, 1931, ii, 565; 617; 669.
2. Dreschfeld, J.: Ulcer of the stomach *in:* A System of Medicine, by many writers; edited by Sir Clifford Allbutt, 1897, Macmillan Company, New York, iii, p. 520.
3. Huber, A.: Über die Heredität beim Ulcus ventriculi Münch., Med. Wchnschr., 1907, liv, 204–207.

4. Czernecki, W.: Über den Einfluss der Heredität auf die Bildung des Magengeschwürs, Wien Klin. Wchnschr., 1910, xxiii, 661–664.
5. Plaut, A.: Über Säurebefunde und Altersverhältnisse bei Ulcus ventriculi, Arch. f. Verdauungskr., 1913, xix, 23–41.
6. Verbrycke, J. R., Jr.: Cases of hereditary tendency to gastric ulcer, Interstate Med. Jr., 1915, xxii, 844–845.
7. Plitek, V.: Über das familiäre Auftreten des Ulcus ventriculi, Arch. f. Verdauungskr., 1914, xx, 461–468.
8. Spiegel, E.: Beiträge zur klinischen Konstitutionspathologie. II. Organdisposition bei Ulcus pepticum, Deutsch. Arch. f. klin. Med., 1918, cxxvi, 45–60.
9. Hurst, A. F., and Stewart, M. J.: Gastric and duodenal ulcer, 1929, Humphrey Milford, Oxford Univ. Press, London.
10. Strauss, H.: Über hereditäres und familiäres Vorkommen von Ulcus ventriculi et duodeni, Münch. Med. Wchnschr., 1921, lxviii, 274–275.
11. Dauwe, F.: L'hérédité de l'ulcère rond de l'estomac, Arch. mal. de l'appar. digest., 1913, vii, 375–383.
12. Mathieu, A., and Moutier, F.: Pathogénie de l'ulcère de l'estomac, Arch. mal. de l'appar. digest., 1909, iii, 445–474.
13. Draper, G., and Touraine, G. A.: Man environment unit and peptic ulcer, Arch. Int. Med., 1932, xlix, 616–662.
14. Bloomfield, A. L.: Clinical aspects of gastric secretion, Ann. Int. Med., 1932, vi, 307–313.
15. Huddy, G. P. B.: A study of the family histories of 300 patients suffering from chronic upper abdominal lesions, Lancet, 1925, ii, 276–278.
16. Wilkie, D. P. D.: Duodenal ulcer in the female; cholecysto-duodenal syndrome, Lancet, 1927, ii, 1228–1231.
17. Menasci, R.: A proposito dell'esistenza d'una predisposizione familiare nelle ulcere gastro-duodenali, Morgagni, 1930, lxxii, 990–998.
18. Ruhmann, W.: Ergebnisse zur Frage der Konstitution bei Ulcus pepticum, Deutsch. Med. Wchnschr., 1925, ii, 2032.
19. Britt: Quoted by Menasci.
20. Zisa, S.: Il fattore costituzionale nella genesi dell' ulcera peptica; ricerche antropometriche, Arch. di pat. e clin. med., 1924, iii, 454–472.
21. Aschner, B.: Über Konstitution und Vererbung beim Ulcus ventriculi und duodeni, Ztschr. f. d. ges. Anat., 1923, ix, 6–46.
22. Bauer, J.: Disposition, 1921, 433.
23. Bauer, J., and Aschner, B.: Konstitution und Vererbung bei Ulcus pepticum ventriculi und duodeni, Klin. Wchnschr., 1922, i, 1250; 1298.
24. Warthin, A. S.: Heredity of carcinoma in man, Ann. Int. Med., 1931, iv, 681–696.
25. (*a*) Perisse: De l'ulcère de l'estomac et de certains accidents gastriques chez les hystériques, Thèse de Paris, 1876.
(*b*) Gilles de la Tourette: L'ulcère rond de l'estomac dans les rapports avec l'hystérie, Semaine méd., 1899, 377.

TOXICOLOGY AND ASSAY OF METHYLENE BLUE *

By DAVID I. MACHT, M.D., F.A.C.P., and WILTON C. HARDEN, PH.D.,
Baltimore, Maryland

INTRODUCTION

METHYLTHIONINE chloride, or methylene blue, is recognized by the United States Pharmacopoeia but its administration has hitherto been only by mouth. Recently, however, considerable publicity has been given its intravenous use in cases of cyanide and carbon monoxide poisoning. This therapeutic application of the dye has been the direct result of the most interesting laboratory investigations of Matilda M. Brooks [1, 2, 3, 4] and clinical reports of J. C. Geiger.[5, 6]

The value of methylene blue in the treatment of cyanide poisoning has been described by earlier writers. Thus, Sahlin [7] demonstrated its antidotal action in 1926, and Eddy [8, 9] also found that methylene blue stimulated the respiration and counteracted the poisonous effects of sodium cyanide. Hanzlik [10] also mentions experimental work on this subject. Gessell, Kreuger, Nicholson, Brassfield and Pelecovich [11] also found that methylene blue, administered intravenously to dogs, furthered their recovery from sodium cyanide poisoning. Warburg and Christian [12] studied the mechanism of this action.

In regard to the effects of methylene blue on carbon monoxide poisoning, the theory upon which Matilda Brooks proceeded in her experiments was based chiefly on the brilliant researches of Warburg,[13, 14] who showed that methylene blue has an action antagonistic to that of CO upon the oxygen consumption of yeast cells. Later, Warburg, Kubowitz and Christian found that the oxygen uptake of red blood cells is practically unaffected by carbon monoxide in the presence of enough methylene blue [15]; and Ambrus, Banga and Szent-Györgyi [16] further found that methylene blue was reduced not only by yeast but also by various animal tissues to methylene white. Cook, Haldane and Mapson [17] found that oxidation of succinate to fumerate, lactate to pyruvate and fumerate to bicarbonate is little affected by CO if methylene blue be present.

Methylene blue has been utilized by biologists for studying oxidation and reduction of the most varied character. That methylene blue increases the oxidation of animals has been shown by the work of many authors, especially that of Heymans and Heymans,[18] Barron,[19] and Harrop and Barron.[20]

Elsner [21] found that methylene blue affects the respiration of plant cells. Watanabe [22] found that the respiration of various algae was stimulated by methylene blue. Sunzeri [23] found that methylene blue, added to dog's liver,

* Received for publication July 5, 1933.
From the Chemical and Pharmacological Research Laboratories, Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.

accelerates lipodieresis. Wieland and Mitchell [24] discovered that methylene blue tended to reduce xanthine. Bertho and Glück [25] established the fact that methylene blue hastened the dehydrogenation of glucose under certain conditions. Wolfson [26] found that this dye affects the production of catalase, and Roffo [27] used methylene blue as a hydrogen acceptor in the treatment of carcinoma. The activation of fermentation of living tissue was further studied by Rosenthal.[28] Very recently, Himwich and his coworkers [29, 30, 31] studied the effect of methylene blue and cyanide on the respiration of the brain, testicle, liver and kidneys, and on the metabolism of rats.

With regard to the pharmacology of this dye, Gregoire [32] noted that methylene blue raises the temperature and profoundly affects the metabolism of rats. Perfusing the dye through the legs of a dog, Bornstein and Pantke [33] found that small doses produced a primary dilatation followed by constriction of the vessels, while larger doses produced an immediate constriction; and a rise in blood pressure with stimulation of respiration after administration of the drug has been described by various authors. Recently, while studying the effects of methylene blue on blood by phytopharmacologic methods, Macht found that this dye antagonizes the poisonous action of carbon monoxide hemoglobin and that it also neutralizes in vitro the toxins of certain diseases, especially that of pemphigus.[34]

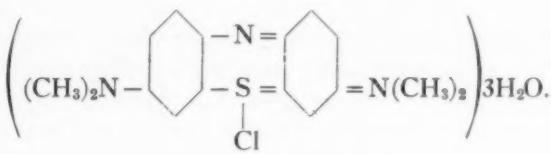
Purpose of the Present Work

The object of the present research was to secure a *reliable* and *safe* preparation of the dye for intravenous injection in clinical cases. Samples of methylene blue on the market were obtained and compared as to their purity and toxicity by chemical and pharmacologic methods. Methylthionine chloride is a complicated organic mercurial. Now it is well known that most dyes intended for commercial and technical uses are contaminated by impurities, or diluted with such substances as dextrose, sodium chloride, sodium sulphate, etc. For intravenous injection in human beings such preparations, of course, are in no wise suitable. It is imperative that a chemically pure drug be obtained for such administration. Furthermore, a search through the literature reveals that the potency of this drug for different animals varies greatly, and that the data gathered by a number of investigators regarding the toxicity of methylene blue for the same species of animal also show a wide divergence, which fact probably indicates variations in the composition of different samples studied by these respective workers. The toxicology of methylene blue has been studied by Meyer,[35] Caseneuve,[36] Ehrlich and Leppmann,[37] Garfounkel and Gautrelet,[38] and other writers. A complete bibliography on the subject is furnished by Fühner's chapter on methylene blue in Heffter's *Handbuch,*[39] and by Flüry and Zernik [40] in Abderhalden's *Handbuch.* The data gleaned from these are confusing and leave the investigator in much doubt as to the purity of the compounds employed, on the one hand, and their correct dosage and toxicity, on the

other. A uniform and simple method of pharmacological assay is therefore much to be desired. In the present work, an attempt is made to clarify this subject for practical purposes.

Chemical Examination

Methylene blue is a tetra-methyl-thionine chloride, having an empirical formula of $C_{16}H_{18}N_3SCl \cdot 3H_2O$. Its molecular weight is 373.4. The structural formula as given by Führer is



We have examined five different samples of methylene blue by chemical methods. Each of these samples, marked " Methylene Blue " or " Methylthionine Chloride, U. S. P., Medicinal," was supposed to be a high-grade product intended for internal use. These specimens were analyzed for their chlorine and nitrogen content in order to obtain an indication as to their purity. The calculated theoretical percentage of chloride in methylene blue is 9.48. The calculated theoretical percentage of nitrogen in the molecule is 11.24. Table 1 shows the percentages of chlorine and nitrogen in the five samples of dye analyzed. It will be noted that the chemical composition of the various samples examined differed greatly and, on analysis, only one of the samples, No. 4, which was a chemically pure product, gave figures approximating those of theoretical calculation. One of the specimens contained 0.48 per cent of inorganic sulphur.

Table I

Specimen of Methylene Blue	Chemical Analysis		Pharmacologic Test
	Per cent of Chlorine (Theoretical, 9.48%)	Per cent of Nitrogen (Theoretical, 11.24%)	Lethal Dose in Milligrams per Kilo Weight of Cats
No. 1	9.18 per cent	10.54 per cent	100 milligrams
No. 2	8.60 per cent	10.30 per cent	51 milligrams
No. 3	19.68 per cent	6.83 per cent	210 milligrams
No. 4	9.38 per cent	11.00 per cent	41 milligrams
No. 4	9.38 per cent	11.00 per cent	54 milligrams (after autoclaving)
No. 5	8.00 per cent	10.85 per cent	75 milligrams

Pharmacologic Examination

A consideration of many discrepancies between the reports of various investigators cited in older literature on the subject made it desirable to test

the potency of different specimens of methylene blue pharmacologically. Toxicologic experiments were made with intraperitoneal injections in mice, rats and guinea pigs, with subcutaneous injections in guinea pigs and with intravenous injections in rabbits and cats. After considerable preliminary investigation, it was found that the most valuable information on the subject could be deduced from carefully planned experiments on cats.

The method of procedure was as follows: Full-grown cats were anesthetized and kept constantly under ether by inserting a tracheal cannula connected with a respiratory bottle. Blood pressure tracings from the carotid artery were made on a slowly revolving kymograph, and tracings of the respiratory movements were obtained by a special method described by one of the authors elsewhere.[41] A cannula was inserted into the femoral vein. A 0.5 per cent solution of methylene blue in physiological sodium chloride was then injected into the femoral vein of the cat at regular intervals from a burette. The effect of the injection of one c.c. of the solution a minute upon the blood pressure and respiration and other functions of the body was noted. It was found that an injection of one c.c. of 0.5 per cent of methylene blue promptly produced a rise in blood pressure, which returned to normal, however, at the end of a minute. Subsequent injections at one-minute intervals produced the same effect, namely, a sharp rise in the blood pressure with return to normal. When the injections were increased in number, however, the rises gradually became less marked and the blood pressure finally dropped suddenly to a dead level. Simultaneously with the rise in blood pressure produced by injections of the dye, a slight stimulation of both the frequency and amplitude of the respiration was noted. When the blood pressure reached the lethal stage, the respiration continued and indeed was stimulated for a minute or two after cessation of the heart-beat. Injections of methylene blue were also found to produce a marked hyperpyrexia or rise of several degrees in the animal's temperature, which could be detected merely by touching its body with the naked hand or be measured with a thermometer. After injection of large doses of the methylene blue, the blood turned chocolate in color and gave evidence of the formation of methemoglobin.

Experiments like those described above were repeatedly made with different samples of methylene blue. The results obtained are exhibited in the foregoing table in which, for the sake of completeness, are also shown the findings obtained on chemical analysis of the different specimens. It was found that the minimal lethal dose of the chemically pure sample of methylene blue, No. 4, was 41 mg. per kilo weight for cats. The minimal lethal doses of the other four samples examined were all greater than that of the chemically pure substance, although all the specimens had been labelled, "Methylene Blue, U. S. P.—Medicinal." In figure 1 is reproduced the kymographic record of one of the experiments. Here are shown the tracings made of the blood pressure, respiratory movements, and also the time on a slowly turning drum.

The Method of Sterilizing Methylene Blue Solutions

Earlier investigators have found that methylene blue itself is antiseptic to a certain degree. We have found that the simplest and safest way of sterilizing such solutions was to boil them for a few minutes over the open flame or to heat them on the waterbath from 10 to 15 minutes. We experimented on the effects of sterilizing the methylene blue solutions in an autoclave under pressure. However, it was found that such solutions underwent

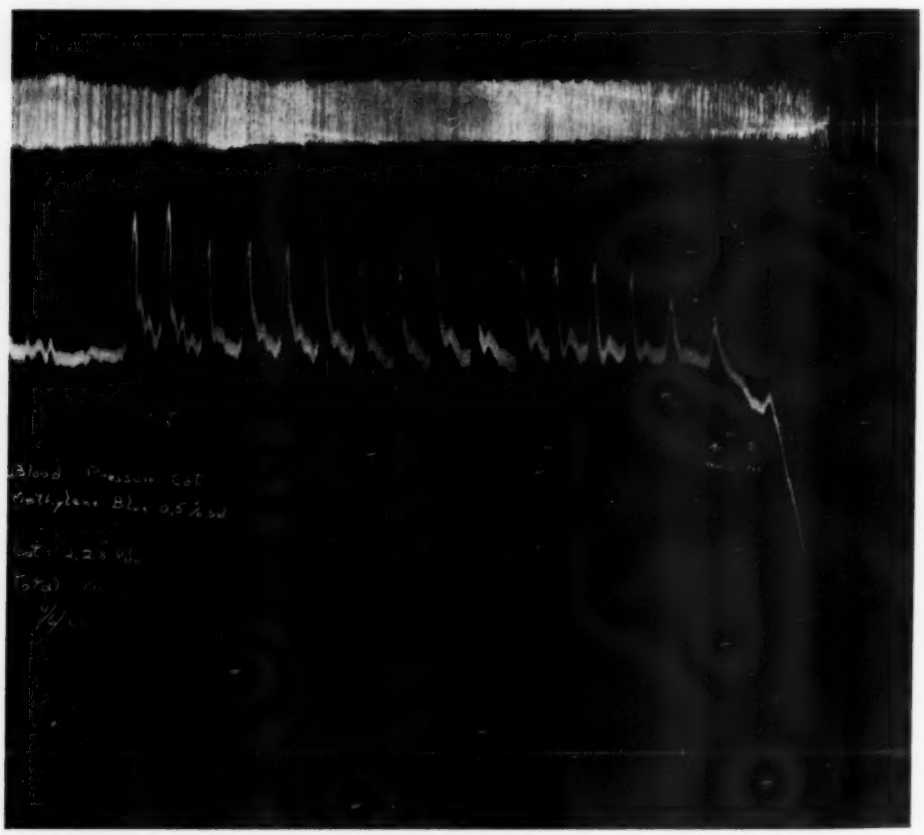


Fig. 1. Intravenous injection of chemically pure methylthionine chloride. Effect on blood pressure and respiration.

considerable decomposition. The dye became demethylated to some extent and yielded methyl alcohol and another dye known as Lauth's violet. A pharmacologic test with such partially decomposed solutions of methylene blue revealed that they were less toxic than the original solution. Thus it will be seen that the average lethal dose for cats of a specimen of methylene blue sterilized in the autoclave was 54 mg. per kilo.

The keeping qualities of solutions of methylene blue are somewhat in

question but we have had no serious difficulties in this respect. After such solutions had been sterilized on the waterbath and boiled, practically no precipitate was noted. However, it has been suggested that solutions of methylene blue, made up with sodium sulphate, may keep better after several weeks have expired. To this procedure there can be no objection because, when injected intravenously, the sodium sulphate in such solutions would tend to lower the toxicity of the dye.

Discussion

The results of pharmacologic experiments not only on cats but also on other animals impress us with the fact that methylene blue, especially when administered intravenously, is by no means an innocuous substance; and the more chemically pure the dye is, the more potent it is pharmacologically. It is furthermore interesting to note that samples of methylthionine chloride on the market, even though labeled, "U. S. P., Medicinal," show marked variations in chemical composition and toxicity. It is therefore very desirable in all pharmacologic and therapeutic experiments with this drug to use a preparation which is chemically pure and which has been assayed in regard to its potency. Without passing judgment on the value of methylene blue as a therapeutic agent in the various conditions in which it has already been advocated and used, it is our opinion that all the results to be expected from its use could be obtained equally well and with greater safety with smaller doses of the dye than those which have been recommended up to the present time in clinical papers on the subject. The recently published studies of one of the writers concerning the effects on living plants of very dilute solutions of methylthionine chloride, and the detoxification thereby of a number of toxins in the blood, corroborate this view. We should not recommend the administration of 50 c.c. of a 1 per cent solution of methylene blue as a single dose for intravenous injection in human beings but rather doses of from 10 to 20 c.c. of a 0.5 per cent solution, which could be repeated if desired.

Summary

1. Chemical and pharmacologic examination of various samples of "medicinal" methylene blue on the market reveals that they differ greatly in their purity.

2. A method of assay of methylthionine chloride for intravenous administration has been described.

3. The lethal dose of chemically pure methylthionine chloride administered intravenously to cats is about 40 mg. per kilo weight.

4. It is suggested that whenever the therapeutic effects produced by methylthionine chloride are desired, the results may be obtained more safely by administering smaller doses of the dye than those which have been recently recommended for intravenous injection.

REFERENCES

1. Brooks, M. M.: Effect of methylene blue on CN and CO poisoning (preliminary report), Proc. Soc. Exper. Biol. and Med., 1932, xxix, 1228–1229.
2. Brooks, M. M.: Effect of methylene blue on HCN and CO poisoning, Am. Jr. Physiol., 1932, cii, 145–147.
3. Brooks, M. M.: Methylene blue as antidote to CO poisoning (preliminary report), Proc. Soc. Exper. Biol. and Med., 1933, xxx, 493–494.
4. Brooks, M. M.: Methylene blue as antidote to CO poisoning, Am. Jr. Physiol., 1933, civ, 139–141.
5. Geiger, J. C.: Cyanide poisoning in San Francisco, Jr. Am. Med. Assoc., 1932, xcix, 1944–1945.
6. Geiger, J. C.: Methylene blue solutions in treatment of carbon monoxide poisoning, Jr. Am. Med. Assoc., 1933, c, 1103–1104.
7. Sahlin, B.: Antagonism between methylene blue and potassium cyanide, Arch. f. Physiol., 1926, xlvii, 284.
8. Eddy, N. B.: Antagonism between methylene blue and sodium cyanide, Jr. Pharm. and Exper. Therap., 1930, xxxix, 271.
9. Eddy, N. B.: Regulation of respiration; antagonism between methylene blue and sodium cyanide, Jr. Pharm. and Exper. Therap., 1931, xli, 449–464.
10. Hanzlik, P. J.: Methylene blue as antidote for cyanide poisoning, Jr. Am. Med. Assoc., 1933, c, 357.
11. Gessell, R., and others: Comparison of response of anesthetized dog to intravenous administration of sodium cyanide during uniform artificial ventilation and during normally controlled ventilation with additional observations on effects of methylene blue, Am. Jr. Physiol., 1932, c, 227–240.
12. Warburg, O., and Christian, W.: Über ein neues Oxydationsferment und sein Absorptionsspektrum, Biochem. Ztschr., 1932, ccliv, 438.
13. Warburg, O.: Über die Grundlagen der Wielandschen Atmungstheorie, Biochem. Ztschr., 1923, cxlii, 518–523.
14. Warburg, O.: Über die Wirkung des Kohlenoxyds auf den stoffwechsel der Hefe, Biochem. Ztschr., 1926, clxxvii, 471–486.
15. Warburg, O., Kubowitz, F., and Christian, W.: Über die katalytische Wirkung von Methylenblau in lebenden Zellen, Biochem. Ztschr., 1930, ccxxvii, 245–271.
16. Ambrus, P., Banga, I., and Szent-Györgyi, A.: Beiträge zur Methodik der Messung des Sauerstoffverbrauchs, des Respirationsquotienten und der Methylenblaureduktion der Gewebe und der Hefe, Biochem. Ztschr., 1931, ccxl, 473–477.
17. Cook, R. P., Haldane, J. B. S., and Mapson, L. W.: Relationship between respiratory catalysts of *B. coli*, Biochem. Jr., 1931, xxv, 534–550.
18. Heymans, J. F., and Heymans, C.: Hyperthermia and increase of the respiratory volume and of the elimination of carbon dioxide produced by methylene blue, Arch. Internat. Pharmacodynamie, 1922, xxvi, 443.
19. Barron, E. S. G.: Studies on blood cell metabolism; effect of methylene blue on oxygen consumption of eggs of sea urchin and starfish; mechanism of action of methylene blue on living cells, Jr. Biol. Chem., 1929, lxxxi, 445–459.
20. Harrop, G. A., and Barron, E. L. G.: Studies on blood metabolism. II. The effect of methylene blue and other dyes upon the glycolysis and lactic acid formation of mammalian and avian erythrocytes, Jr. Exper. Med., 1928, xlviii, 207.
21. Elsner, W.: Action of methylene blue on living plant cells, Ztschr. f. Wissensch. Mikr., 1932, xlix, 28.
22. Watanabe, A.: Physiology of the metabolism of algae. I. Influence of potassium cyanide and methylene blue on the respiration of some green algae, Acta phytochim., 1932, vi, 315.
23. Sunzeri, G.: The action of certain photodynamic substances on lipodieresis, Boll. d. Soc. ital. di biol. sper., 1932, vii, 740.

24. Wieland, D., and Mitchell, W.: Mechanism of oxidation processes. XXIX. Dehydrogenating enzymes of milk, Liebig's Annalen, 1932, cdxcii, 156.
25. Bertho, A., and Glück, H.: Respiratory processes of lactic acid bacteria, Liebig's Annalen, 1932, cdxciv, 159.
26. Wolfson, I. A.: The influence of dyes on the formation of catalase in certain bacteria, Arch. sci. biol. (U. S. S. R.), 1931, xxxi, 161.
27. Roffo, A. H.: Oxydo-Reduktion in der Krebsbehandlung, Ztschr. f. Krebsforsch., 1932, xxxvii, 1–9.
28. Rosenthal, O.: Versuche über die Aktivierung der anaeroben Gärung von Lebergewebe durch Brenztraubensäure, Acetaldehyd und Methylenblau, Biochem. Ztschr., 1932, ccxliv, 133–156.
29. Himwich, H. E., Fazikas, J. F., and Hurlburt, M. H.: Effect of methylene blue and cyanide on respiration of cerebral cortex, testicle, liver and kidney, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 904–906.
30. Himwich, H. E., and Goldfarb, W.: Effects of methylene blue on respiratory metabolism of rat, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 906–907.
31. Himwich, H. E., and others: Effect of methylene blue on R. Q. of brain in situ, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 907–908.
32. Gregoire, P. E.: Action of methylene blue on body temperature and metabolism, Jr. Exper. Med., 1931, liv, 827–845.
33. Bornstein, A., and Pantke, R.: Die Gefässwirkung des Methylenblaus, Arch. f. exper. Path. u. Pharm., 1931, clxi, 229–232.
34. Macht, D. I.: Effect of methylthionine chloride on phytotoxic reaction of normal and pathological blood, Proc. Nat. Acad. Sci., 1933, xix, 486–491.
35. Meyer, S.: Die subcutane Methylenblauinjection, ein Mittel zur Darstellung der Elemente des Centralnervensystems von Säugethieren, Arch. f. mikr. Anat., 1895, xlvi, 282–290.
36. Caseneuve: La coloration des vins, Paris, 1886, 89.
37. Ehrlich, P., and Leppmann, A.: Über schmerzstillende Wirkung des Methylenblau, Deutsch. med. Wchnschr., 1890, xvi, 493.
38. Garfounkel, I. G., and Gautrelet, J.: Contribution à l'étude de l'action des matières colorantes sur la coeur et la pressure, Compt. rend. Acad. d. sci., 1913, clvii, 1464–1466.
39. Führer: Handbuch der experimentellen Pharmakologie, A. Heffter, Berlin, 1923, i, 1268.
40. Flüry, and Zernik: Handbuch der biologischen Arbeitsmethoden, Emil Abderhalden, 1928, Abt. IV, Teil 7, Heft 7, Lieferung 251, 1366.
41. Macht, D. I.: A simple method of studying respiratory pharmacodynamics, Jr. Am. Pharmaceut. Assoc., 1930, xix, 7.

CONSERVATISM, THE KEYNOTE IN THE TREATMENT OF TUBERCULOSIS*

By C. H. Cocke, M.D., F.A.C.P., *Asheville, North Carolina*

When a diagnosis of pulmonary tuberculosis has been made, the planning out of a mode of treatment entails considerably more than the immediate relief of the presenting symptoms. To attempt a finally definitive outline at once, and particularly to essay a prognosis until more is known of the case, is hazardous and will frequently bring disappointment. Hasty judgment in all medical matters is to be deplored; in tuberculosis it is to be condemned in no uncertain terms.

To begin with, it must be insisted that the tuberculous patient presents a problem that is quite different from that found in most chronic diseases. Any plan of treatment that may be expected to offer hope of arrestment, if not full recovery, must be predicated upon the assumption of the patient's willingness and ability to see it through. In any such plan, time is of the essence, time and more time; and most efforts to shorten unduly this element end in disappointment and frequently in disaster. Other variable factors which make the treatment of the tuberculous an engrossing and ever changing challenge are the patient's age, his social and economic background, his disposition, temperament, and character, his patience and courage and willingness for sacrifice of time and family, his intellectual background and resources for harmless interests and entertainments, his habits of life and habits of thought, his spirit of coöperation or rebellion, and particularly the imponderable factors of the reaction of the individual host to the given invader. While it is fairly well known what happens when the tubercle bacillus invades the human organism, whether for the first time or for subsequent attack, this knowledge does not extend to any degree of certainty as to what will happen in any given case of *clinical tuberculosis.* The mere matter of the geographical location of the tuberculous lesion, or the chance occurrence of a complication, may make what started out as an apparently harmless or mild disease suddenly become an extremely severe and disabling one! The addition of an acute respiratory infection leaves one case that was only mildly active sadly reactivated; and apparently a similar case, with like accident, goes on to an uninterrupted arrest, as though nothing unusual had happened. A small hemorrhage occurs, and a previously sluggish lesion apparently makes more rapid and satisfactory progress; another hemorrhage may be followed by miliary spread of the disease. One could go on at length with the recital of the uncertainties of the progress of any given case of tuberculosis, as compared with any other given case of *apparently similar* extent and kind. In the end, one must conclude that each

* Presented before the General Session of the American College of Physicians, 17th Annual Session, Montreal, Canada, February 8, 1933.

individual case of tuberculosis is in some measure *sui generis;* and, for successful treatment, must be studied and managed as a separate and individual problem, with only certain fundamental factors in the treatment known. Tuberculosis, as a disease, cannot often be successfully treated; *patients* with tuberculosis can and are treated successfully by the thousands. The art as well as the science of medicine must be applied; mere science in this instance is rarely enough.

In no other disease is the problem of the assay of the results of treatment more difficult than in tuberculosis. As each case is, as I have stated, a law unto itself, the difficulty of obtaining control observations is well nigh insuperable, as there is no sure way of selecting comparable controls. So many cases get well with only rest treatment, and that sometimes in the sketchiest of forms, that one should pause before attributing to any specific added form of treatment the success finally achieved. Hence the futility of attempting, for instance, to evaluate the effect of climate and rest as compared with that of compression and surgical procedures. Such comparisons do not fall within the purpose of this paper. Its purpose is rather to attempt to demonstrate the truth of a principle which I feel is fundamental in the treatment of any given case of tuberculosis, namely that of all the measures that up to the present time have been given a trial, *rest is the only specific;* and that conservatism in the management of the case is generally rewarded.

Some years ago Dr. Robert T. Morris pointed out that surgery had gone through four evolutionary eras: the Homeric period of its earliest efforts; the roughly Anatomic period; the Pathologic period (based on Virchovian cellular pathology); and the present day Physiologic era, in which the surgeon's dual purpose is the eradication of pathologic processes and the restoration of physiologic function. Quite similarly the treatment of tuberculosis may be said to have passed through certain well defined phases.

Perhaps the first successful effort at treatment of tuberculosis was made by Brehmer and Dettweiler. Theirs, however, was only a partial success, for Brehmer to the end maintained that *exercise* was the curative factor, while Dettweiler found the sovereign factor in fresh air; both failed to realize that the rest they gave their patients *incidentally* was in all probability the chief factor in their success. Of the Climatic era, at least in this country, little need here be said. It is sufficient to observe that even if at present no man claims that climate alone will cure tuberculosis, he would be more than rash who claimed that there were not certain climates inherently beneficial to the tuberculous. As Lawrason Brown insists, almost any change helps the tuberculous patient; and, if that change can be to a locality or climate where the pursuit of his cure is made more easy and certain, so much the better for the patient. My own position in the matter can be summed up in the aphorism, *it is infinitely more important what the tuberculous patient does than where he does it,* or as Osler phrased it, " care without climate is better than climate without care."

The Tuberculin era followed, and in its wake came a series of biologic

and chemotherapeutic efforts that have all fallen short of success. Today in treatment tuberculin has, in my opinion, an extremely limited application; in diagnosis, it is an invaluable measure. Of the chemicals, gold and sodium thiosulphate, Sanocrysin has perhaps met with more success than any other, and yet its use is quite limited, and it is a hazardous drug improperly applied.

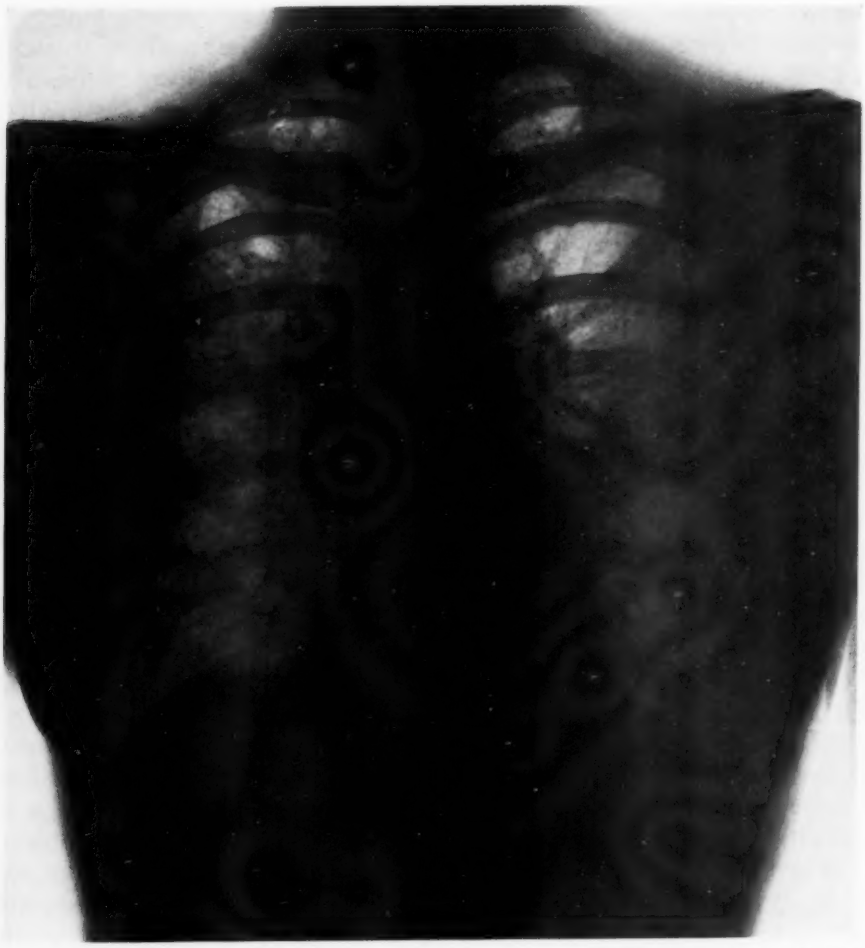


FIG. 1. *Case I.* T. M., female, age 23. July 11, 1928. Marked, right-sided infiltration; cavity second interspace; left lower lobe infiltration.

The Sanatorium and Rest era (for the latter became possible because of the former) gave us our first real conception of the true nature of the healing factor in the cure. Recently Pratt of Boston has well traced the evolution of the rest cure in tuberculosis, and I can add nothing to his interesting paper. It is scarcely necessary to expand upon the value of rest; it remains, as Krause has well insisted, *the only proved specific* in the treatment of the disease.

The Compression era was started by a growing knowledge of the value of Forlanini's work in pneumothorax. Of external appliances for attempted immobilization, shot bags, pneumatic jackets, postural rest, etc., it need only be said that they all have as their chief function an effort to put the diseased lung at rest. The same statement is true likewise of the various surgical

FIG. 2. *Case I.* T. M. June 14, 1930. Complete clearing by resolution of practically all pathology.

procedures now daily practiced wherever tuberculosis is intelligently treated; of internal pneumolysis, which allows the collapse of cavities held open by adhesions; of apicolysis; of paraffin packs; of phrenic crushings or exairesis; of intercostal and other neurectomies; of thoracoplasties, et id al. All such procedures attempt to obtain as much immobilization of the diseased lung

as the operation can accomplish and the patient's lesions will permit. We are in an era of phthisiotherapy by surgery; but in spite of the popular acclaim of these surgical measures it is well for us to pause and consider before we decide to place the treatment of tuberculosis in the domain of the surgeon.

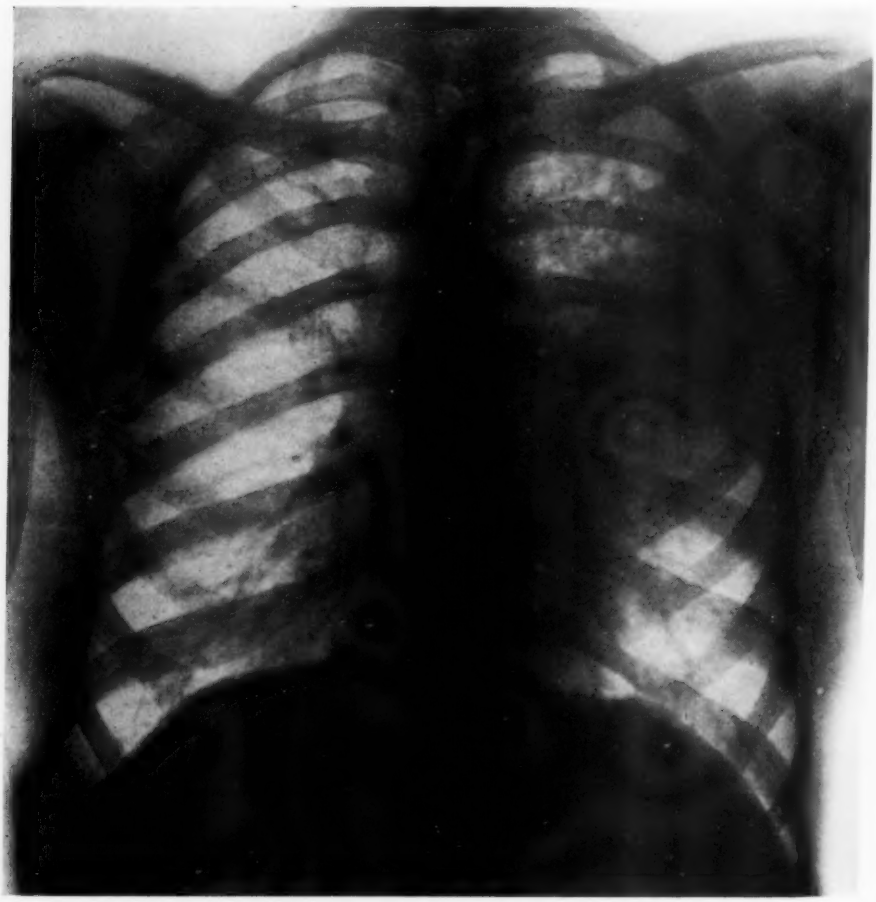


FIG. 3. *Case II.* C. W. M., male, age 24. Fairly acute fulminant history of six weeks. October 2, 1926. Complete left-sided tuberculous involvement; cavity in second interspace; pneumonic consolidation midfield; slight extension to right upper.

In any discussion of compression therapy it should be recognized as a fundamental fact that artificial pneumothorax, which was the first successful compression method developed, when technically possible, is still the most successful and has the widest usefulness. In my opinion it is the one single, most brilliant advance in the treatment of tuberculosis in the past 25 years. It has been, and should be, considered entirely a medical practice as distinct from a surgical procedure, though obviously it should always be done with

the best surgical aseptic technic. With advancing knowledge and accumulating experience, artificial pneumothorax has today a much wider field of usefulness and application than was thought possible in earlier days when its use was restricted to cases showing almost absolute freedom from disease of the contralateral lung. Experience daily shows that fairly widespread

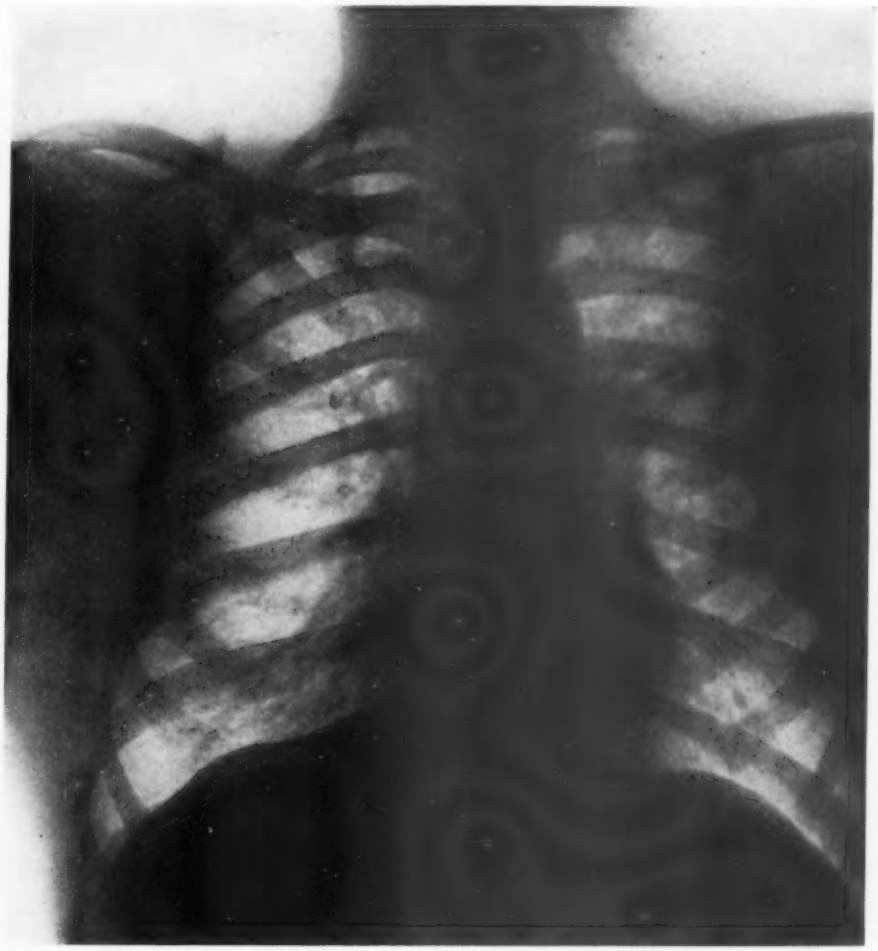


FIG. 4. *Case II.* C. W. M. October 2, 1929. Complete disappearance of cavity. Slight fibrosis in area of former consolidation.

lesions in the opposite lung undergo marked absorption and healing, when the more badly diseased lung has been compressed and the burden of its toxins removed. Laryngeal complications, when amenable to cauterization or other competent treatments, no longer bar us as formerly from its use. This is not the place to attempt a recital of the indications for pneumothorax therapy and the choice of suitable subjects; but it does seem proper to state

that it is the almost universal tendency among the phthisiologists of today to employ artificial pneumothorax earlier and earlier in the disease. The purpose is threefold: to stop the destructive effect of the lesion and arrest its spread; to avoid the danger of a possible later inability to use the method because of pleural symphysis; and lastly to shorten the cure. This is an essentially conservative position to take on this question though I admit that

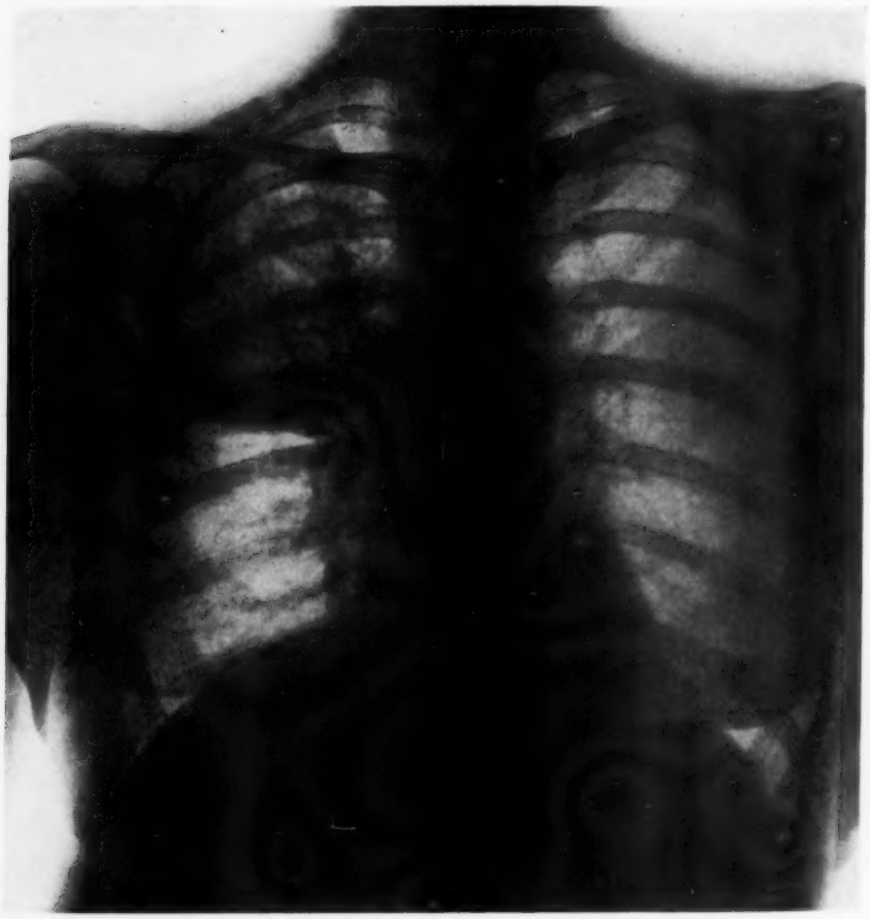


FIG. 5. *Case III.* Mrs. B. M. H., age 57. June 19, 1926. Complete right-sided involvement, fibrocavernous; definite cavity in upper lobe; suggestive one in lower.

as recently as 10 or possibly 15 years ago it might have been considered truly radical.

In taking up now the subject of surgical compressions it is not my object to attempt disparagement or criticism, but rather to present a plea for a proper appreciation of the value of these procedures and particularly for calm and critical judgment as to the proper time for using surgical aid. There is

undoubtedly a tendency among many to resort to surgery earlier and earlier in the disease, until I fear the danger point has been reached of assuming that surgery is a *substitute* for conservative treatment. A denial of this is my major thesis. I cannot offhand agree to the recently expressed surgical opinion that at least 75 per cent of the cases of pulmonary tuberculosis with

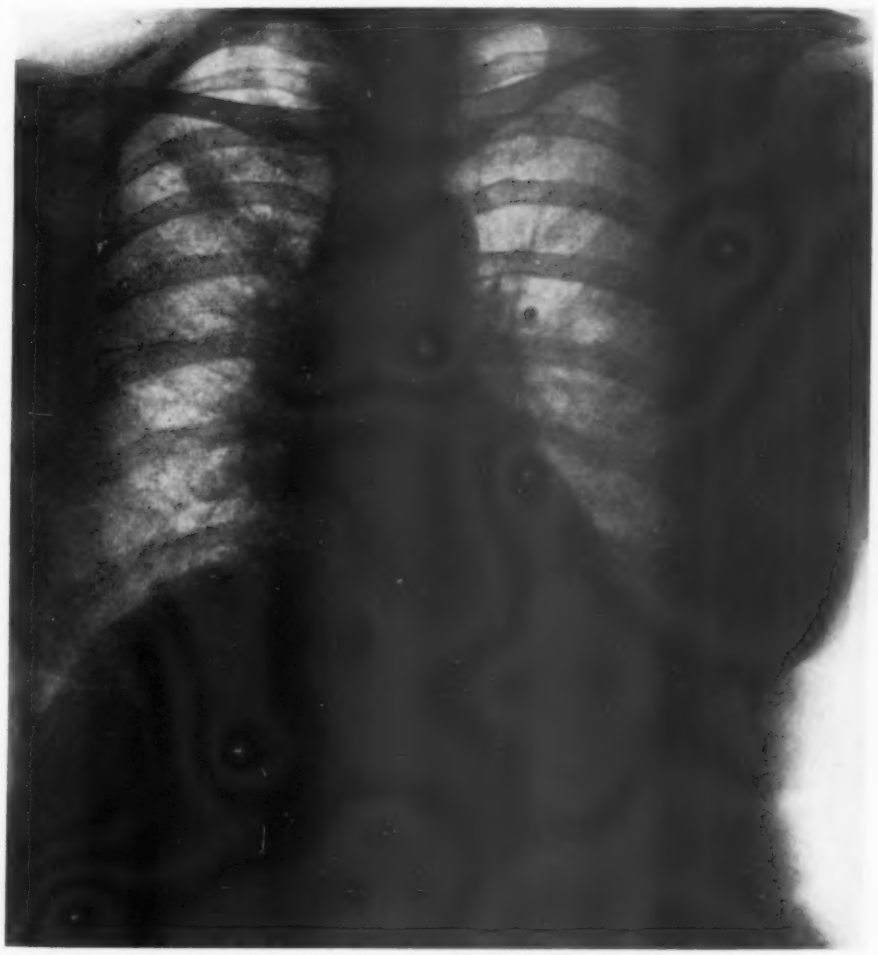


FIG. 6. *Case III.* Mrs. B. M. H. September 20, 1927. Complete clearing of all pathology save slight fibrous band.

cavities should undergo some form of collapse therapy as early in the course of the disease as possible, for the very apparent reason that I know of no possible way of judging at the outset of treatment which case is to be the lucky one in four that will not require compression; nor have I heard of the proper rule for such discovery being given by our surgical colleagues. No one can presume to state categorically how extensive a tuberculous lesion can and will

be resolved or fibrosed and thus healed. With the patient under conditions of ideal basal bed rest, under constant supervision, and radiographic control, I maintain that it is much better to wait and see what happens, rather than hastily to undertake surgical measures which may be needless. This period of waiting does not have to be long; perhaps a month's observation may con-

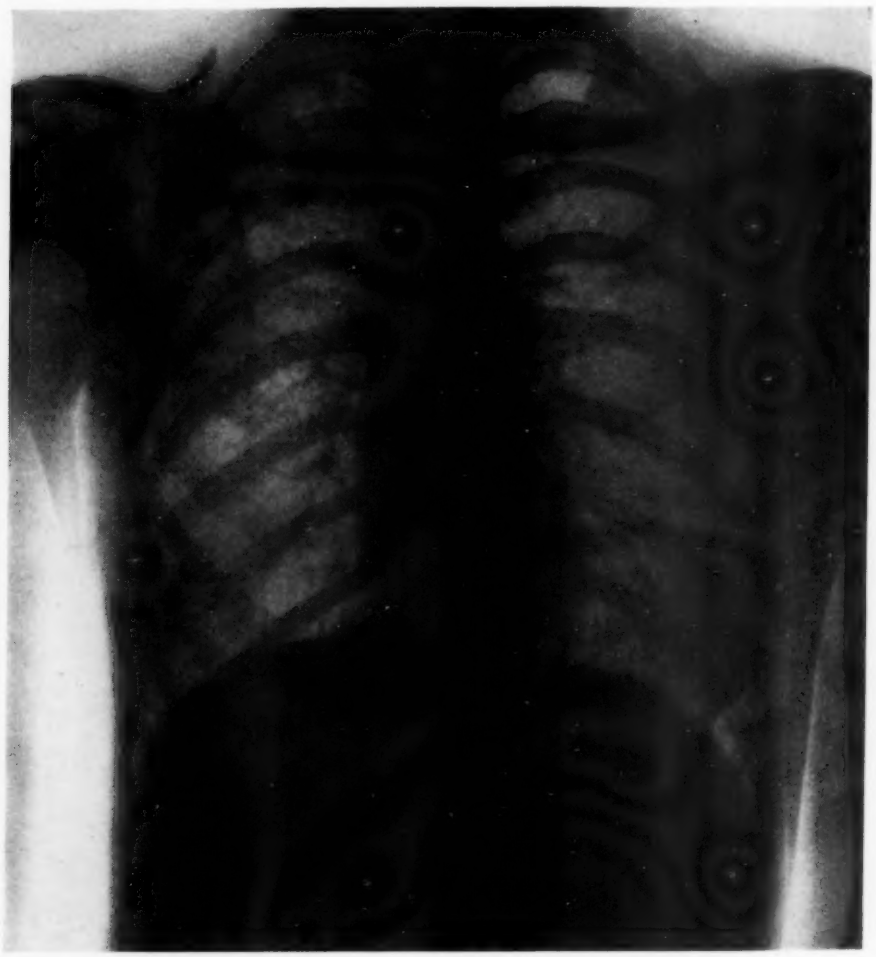


FIG. 7. *Case IV.* Mrs. I. P. B., age 26, weight 93 pounds. May 19, 1926. Tuberculous infiltration and cavitation right upper lobe. Well marked wall to cavity.

vince one of the satisfactory turn of the case, or on the other hand of the inadvisability of further delay in resorting to some form of compression. More likely it will prove best to extend this period of careful waiting to from three to six months, at the end of which time decision as to the best course to follow is made with greater surety. Naturally, this program is predicated upon control of the case immediately after the diagnosis is made, because

it is quite obvious that if any great amount of time has elapsed before the patient comes under treatment there must be some modification of the above outline. Is this delay justified? In my experience it is not only justified, it has proved its value. In tuberculosis we are dealing with a problem that involves not only the patient's present but his entire future existence and activities; and it is important that the method of treatment selected

FIG. 8. *Case IV.* Mrs. I. P. B. June 10, 1927. Cavity still definitely seen.

should not only give him the best help in arresting his disease but should also be the least likely to leave him with an aftermath of crippling handicaps.

A really fundamental objection to surgery in the beginning of treatment is that it is apt to give the patient an exaggerated idea of the efficacy of the surgical procedure and to diminish his appreciation of the value of the proper sort of rest and care, such as is necessary for a good many months after the

operation. Surgery does not cure tuberculosis. At best it puts the diseased lung at rest, and attempts a mechanical closure of cavities which nature has failed to obliterate. Such being the case, no matter how brilliant the mechanical result of the surgical procedure, if the lesions are to heal much time must be given by the patient to the proper régime. The rapid subsidence

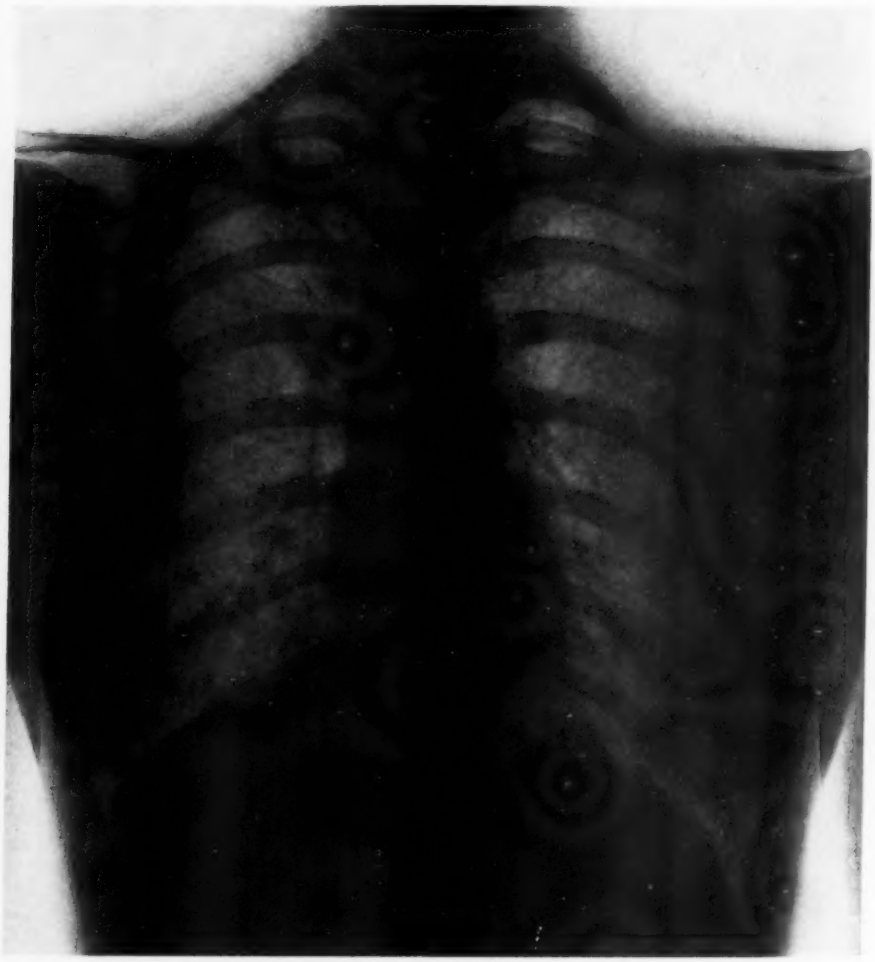


FIG. 9. *Case IV.* Mrs. I. P. B. October 24, 1929. Weight 133 pounds. Complete disappearance of cavity with absorption of most of its wall.

of symptoms gives the untrained patient a false sense of security that leads him inevitably into dangerous overactivities; and as a consequence he may lose the real benefits he should have derived from the operation.

Throughout this discussion, I am speaking entirely from the standpoint of an internist dealing with a referred clientele of tuberculous patients of various origins; and my remarks are not in any sense to be construed as an

effort at solving the question of the best socio-economic approach to the problem of tuberculosis therapy. I can readily appreciate the zeal and enthusiasm for attempted shortcuts in therapy on the part of those dealing with large numbers of patients unable for economic or other reasons to follow the program I advocate. I am speaking of what I conceive to be the best method of approach in handling the private tuberculous patient who comes under my care.

In favor of phrenic section as a mode of compression therapy it is urged that the operation is a simple one, whether a temporary crushing is done, a section, or an exairesis; that it rarely has serious consequences or complications; and that while it formerly had as its main field of endeavor the closures of basal cavities, its benefits are now known to extend to upper lobe cavities and also to soft lesions not yet excavated. I am not disposed to attempt to refute these statements; but when it is claimed further that it should be used in earlier and still earlier lesions, as it is in these that it demonstrates its greatest benefits, I feel that it must be pointed out that it is precisely in these same early cases that careful bed rest and supervision achieve their most brilliant results! The theory of the above argument is well enough; unfortunately in actual practice the results do not justify the glowing claims of some enthusiastic neurectomists. Even in theoretically ideal cases, I have seen the effect of phrenic section exactly nil; and such an outcome is always a serious discouragement to the patient. I believe it is always a mistake to undertake any form of compression therapy (and this is doubly true with respect to pneumothorax) with the patient convinced that in the special procedure lies his salvation. He should be carefully told what to expect, both in the matter of help and in that of possible failure, else his morale may be upset in a way that may have serious consequences. Of phrenicectomy as an aid in pneumothorax, or perhaps as an antecedent of thoracoplasty, I can speak with more enthusiasm. In the release of the so-called suspended cavity, as well as to fortify an expanding lung, where pneumothorax is to be abandoned, voluntarily or necessarily, I believe it has one of its major indications.

The question of thoracoplasty at once brings up a matter that has been often emphasized, but cannot be stressed too greatly. I refer to the necessity for thorough teamwork between a capable internist and a well trained thoracic surgeon. Competency in general and abdominal surgery by no means predicates adequate equipment to do first-class thoracic surgery. Even with the best of training, moreover, the chest team will arrive at the wisest solution of the surgical problem in any given case only through joint study and the closest of coöperation. In this special field, as I insisted earlier, the needs of each patient are highly individualized. The choice of the proper operation, the optimum time therefor, the after care, all require the most thorough collaborative study. Though in the best clinics, the immediate operative mortality rate has been lowered below 5 per cent, thoracoplasty is necessarily such a major procedure that it must not be resorted to

in cases in which there is a question of the cardiovascular system's ability to meet the stress and strain it entails; nor should it be undertaken until less hazardous forms of compression (such as pneumothorax) have failed. Again I would emphasize that the most brilliant surgical procedure does not cure tuberculosis; it merely helps mechanically to close cavities which would

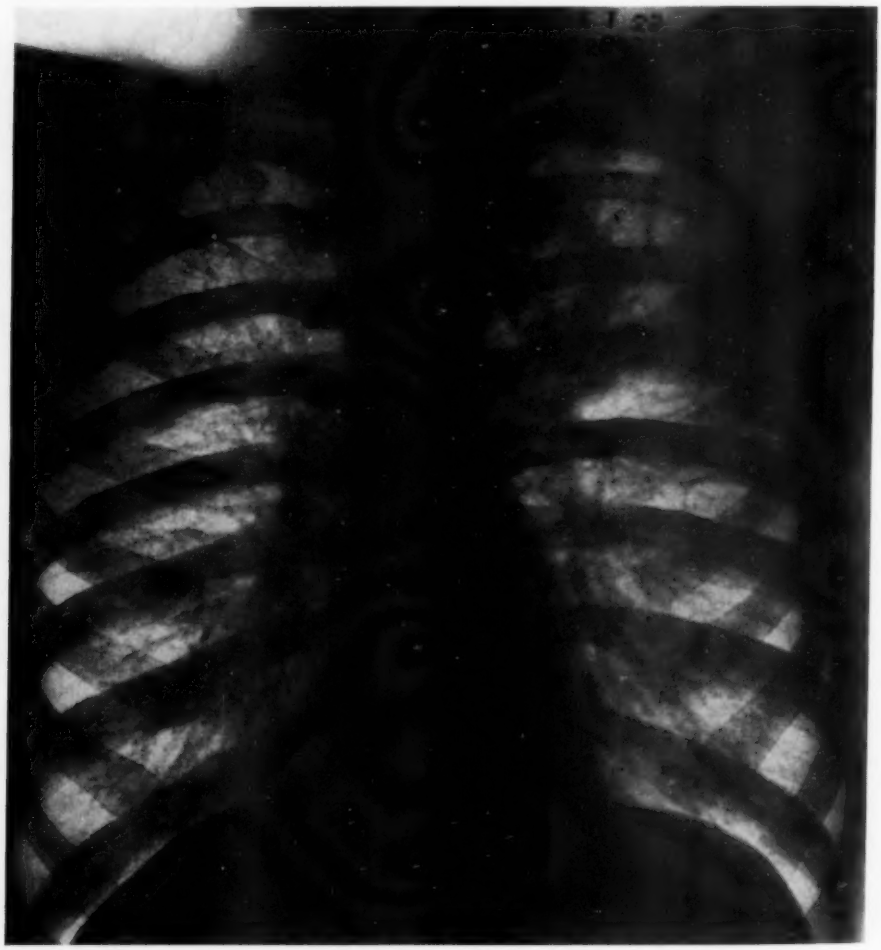


FIG. 10. *Case V.* Dr. H. E. W., male, age 31. April 1, 1929. Left upper lobe cavity, with infiltration. Slight right spread.

otherwise remain open and to give to the diseased lung that rest which is essential for healing. My excuse for this reiteration is the necessity for impressing upon the patient that the tuberculous lesion is there just as it was before the operation, and that time alone can cure him. The operation is *not a substitute for the healing process but an aid thereto.* In properly selected cases, operated upon at the proper time by a competent thoracic

surgeon, we may confidently look for results not achievable by conservative measures alone; but time and careful observation are essential in the choice of patients, the time of operation and its kind, all matters for individual decision upon the merits of the given case.

What may one expect of this expectant and conservative approach to the problem? By conservatism, I mean the intensive application of bed-

FIG. 11. *Case V.* Dr. H. E. W. February 6, 1930. Complete disappearance of cavity, with only fibroid scars remaining.

rest sanatorium care, with all which that implies. I am not disposed to enter into debate about the relative merits of home and sanatorium régime. I am so definitely convinced of the superiority of the sanatorium that I feel most of the objections thereto are academic; and I think this expresses the view very widely held by most men doing tuberculosis work. Naturally, what happens in a given case depends largely upon the time at which the

disease is recognized as well as the extent and the kind of involvement. Far advanced, bilateral disease, with marked proliferative changes and destructive lesions, offer scant hope of more than amelioration at best, no matter what treatment is pursued. Yet here I should like to state one conviction that grows with the years in tuberculosis work: that astonishing things will happen in apparently hopeless cases with sufficient frequency to warrant the statement that every patient with any measure of reserve left should be given the benefit of careful observation before an utterly hopeless prognosis is pronounced. I do not feel that an extensive, one-sided tuberculosis, even with definite cavitation discovered at my first examination, is warrant necessarily for immediate compression therapy. I do feel that such a finding is an indication of delayed diagnosis, whosever the fault, rather than one for surgery. That such conditions heal very frequently without compression of any sort I have frequently seen demonstrated in my patients (Cases 1 to 5, figures 1 to 11). The process of repair is largely a matter of absorption and resolution and to a lesser extent of fibrosis. It is now fairly generally recognized that the symptoms which bring the patient to treatment for tuberculosis are the result of fairly fresh invasions of the bacillus into allergized fields in the lungs. As such, a good part of the pathologic process then represents an exudative or inflammatory lesion. Such lesions, unless quite virulent and aggravated by physical activity on the patient's part, quite frequently resolve under *proper rest.* Will caseous lesions heal? Here we come upon a vexed and difficult problem. The first difficulty is one of definition or, perhaps better, of interpretation. Certainly, lesions which give the physical signs indicative of caseation and the roentgenological appearance thereof (as we at present use these terms) can be seen to melt away and disappear in the serial films. Again, caseous lesions can be replaced by fibrosis; and certainly many so-called fibrous lesions in the films are seen to change and disappear; so that either fibrocaseous lesions resolve, or the time has come to clarify and change our nomenclature or conceptions of tuberculous pathology.

What of the cavity? Can it heal unless compressed? Undoubtedly, and in a great many more instances than could even have been hoped for some years ago. The interpretation of annular shadows may at times be open to question but in many instances in which these rings in the films were accompanied by unequivocal evidence in the patient of the presence of a cavity they have been seen to disappear without resort to any sort of compression therapy. Coryllos' recent observations, before the last meeting of the National Tuberculosis Association, upon the rôle of atelectasis in tuberculosis, are here much to the point. It may well be that atelectasis is produced not infrequently by closure of the bronchus leading into a cavity. There may be no harmful accumulation of sputum, and the resulting anaerobic state may exert a direct inhibiting effect upon the tubercle bacillus, which is a well known aerobe. It is possible that anoxemia stimulates fibrosis. Certainly all clinical observation has proved that the two methods

of healing in tuberculosis, resolution and fibrosis, can and do go on simultaneously, though not necessarily *pari passu*.

Occasionally a patient on the dietetic, hygienic rest treatment alone achieves an astonishing cure by enormous fibrous and calcium deposits. How this last is accomplished I cannot say. Certainly, it is not so fortuitous a method of cure as resolution for reasons too obvious to mention; nor do blood calcium studies throw any particular light on the subject. Certainly raising the patient's blood calcium has not produced such a result.

If a patient under sanatorium care for three to six months at complete bed rest fails to gain or shows evidence of extension of his lesion; if the major lesions are fairly well confined to one lung; if there are no contraindicating complications of tuberculous or other nature, then I think some form of compression therapy is indicated. First, I try pneumothorax; because it is safe, because it can usually be controlled and stopped if necessary, because its major disadvantages can be minimized with care, because it is not shocking, because its benefits are usually so apparent to the patient that he is easily convinced of its value, and because its results are frequently brilliant. Should pleural union prevent the injection of air or a satisfactory collapse, then I usually resort to phrenicectomy. Though certain cavities may be held open by string-like pleural bands, these may be severed after the manner of Jacobaeus or Matson, and a satisfactory collapse be obtained. Persistence of an open cavity and bacillary sputum, after such a procedure in a patient whose lesions are chiefly unilateral, whose general physical condition is good and whose circulatory system is competent, may then indicate the need of either apicolysis, tamponade, or thoracoplasty, as decided upon by the surgeon-internist team.

THE EFFECT OF PILOCARPINE ON THE VOLUME, FREE AND COMBINED ACID, TOTAL CHLORIDES AND PEPSIN OF GASTRIC SECRETION; AND A COMPARISON WITH THE EFFECTS OF HISTAMINE STIMULATION *

By Leo. J. Meienberg, M.D., and Charles L. Brown, M.D., F.A.C.P.,
Ann Arbor, Michigan

A study of the effect of pilocarpine on the various constituents of the gastric juice has been made. The results have been compared with those obtained following histamine stimulation.

Material

Studies were made in 13 cases. These included four normal people, four cases of pernicious anemia, two duodenal ulcers, one gastric carcinoma and two functional cases.

Methods

All subjects were studied under fasting conditions, the fast beginning after the evening meal on the previous day. A Rehfuss tube with an olive tip was used for aspiration. A method of continuous aspiration by means of a water pump was employed, as described by Engelbach and Brown.[1] Care was taken that no saliva was swallowed by the patients during the test and in the event that the juice became bile-tinged the test was discarded. Sievers and Cook,[2] as well as others, have demonstrated that practically complete evacuation of the gastric contents was obtained by means of the Rehfuss tube. In view of this fact it was felt that quantitative studies based on the volume of secretion could be made, inasmuch as continuous aspiration was employed which would prevent any appreciable loss through the pylorus.

The fasting juice was collected for a period of at least 15 minutes in all tests. In eight cases histamine was then given hypodermically and the gastric juice collected for an hour, and in these cases this was followed by a hypodermic injection of pilocarpine and the collection of juice for another hour. In the other five cases pilocarpine was given first and an hour's secretion collected, followed by histamine in the same manner. Nothing was given by mouth during these periods. Polland [3, 4] has shown that the effect of histamine stimulation of gastric secretion ceases within an hour's time, and we were able to confirm this observation in our preliminary experiments with both histamine and pilocarpine. Thus it seems probable

* Received for publication April 12, 1933.
From the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Table I
This Table Shows the Volume, Acidities, Total Chlorides, Peptic Activity, and Total Peptic Activity of the Various Specimens

TABLE I

This Table Shows the Volume, Acidities, Total Chlorides, Peptic Activity, and Total Peptic Activity of the Various Specimens

Case Number	Age	Weight Pounds	Sex	Volume			Free HCl			Total Acid			Total Chlorides			Pepsin Total Activity			Pepsin Maximum Activity per c.c.		
				F	H	P	F	H	P	F	H	P	F	H	P	F	H	P	F	H	P
Normal Individuals																					
5	24	145	M	13	195	21	28.4	37.0	41.4	37.1	41.4	50.1	75.6	84.8	91.6	4312.1	99255.	10126.2	331.7	509.	482.2
6	24	145	M	44	85	52	—	48.8	43.6	15.3	55.3	54.4	80.2	84.8	102.2	9719.6	44319.	22656.4	220.9	521.4	435.7
7*	25	175	M	22	21	130	14.2	15.2	26.2	44.7	26.1	34.9	75.6	95.8	77.0	11814.	19336.8	62010.	537.	920.8	477.
8*	24	150	M	50	116	200	—	43.6	8.7	13.8	54.4	17.4	89.6	80.2	61.4	9050.	43674.	59260.	181.0	376.5	296.3
Pernicious Anemia																					
3	59	100	F	7	2.5	19	—	—	—	not estimated			not estimated			889.7	293.	3426.1	127.1	117.2	313.9
4	56	132	F	0	7	6	—	—	—	not estimated			not estimated			—	3266.2	1791.6	—	464.9	298.6
9	55	88	F	24	31	21	—	—	—	.4	.4	.4	94.4	108.4	110.0	—	—	—	—	—	—
10*	48	140	M	16	21	21	—	—	—	4.4	4.4	2.0	92.8	51.8	45.6	281.6	2070.6	695.1	17.6	98.6	33.1
Duodenal Ulcer																					
2	35	119	M	33	72	35	26.2	56.1	42.6	32.7	66.6	54.5	114.6	133.3	142.4	9840.6	35172.0	19944.2	298.2	533.1	658.9
11	45	145	M	20	81	120	—	12.9	8.6	8.6	27.9	22.6	83.2	77.0	67.6	11312.	69684.3	62004.3	565.6	860.3	516.7
Carcinoma of Stomach																					
13*	64	110	F	6	76	170	—	—	—	not estimated			not estimated			492.	988.	680.	61.0	13.0	4.0
Functional Disease																					
1	14	86	F	15	55	19	32.7	65.5	67.6	39.4	72.1	80.7	118.0	126.4	143.8	5299.5	18309.5	6836.2	353.3	332.9	359.8
12*	34	129	F	110	45	110	28.9	34.4	35.4	42.9	50.5	41.8	not estimated			52723.	38074.5	101695.0	479.3	846.1	924.5

* Pilocarpine given first.
20′–30′ specimen only.

F = Fasting specimen.
H = After histamine (1 hour period).

P = After pilocarpine (1 hour).

that the secretion obtained during our second hour was not influenced by the drug which was given first.

The dosage of histamine phosphate used was 0.1 mg. per 10 kg. of body weight, while pilocarpine nitrate was given in dosages of 0.5 mg. per 10 kg. of body weight.

The gastric juice was collected and studied in three fractions which were designated: *fasting, after pilocarpine* and *after histamine.*

In this manner, in addition to estimating the stimulating effect of these drugs in terms of the maximum concentration during a given period, quantitative determinations of pepsin and volume secretion were estimated; also the acidity and total chlorides were determined on the fractions and the quantities of each of these for the period could be calculated. This would seemingly offer a quantitative index of gastric function.

The volume of each specimen was measured. Free and total acidities were estimated by means of Töpfer's dimethyl indicator and phenolphthalein. Total chlorides were determined by the method of Van Slyke [5] and pepsin estimations were made according to the method of Polland and Bloomfield.[6] In the latter determination the peptic activity per c.c. was multiplied by the volume of the specimen in c.c. to obtain total peptic activity. This figure was used as a basis of comparison also, in addition to the values for maximum peptic activity per c.c.

TABLE II

PEPTIC ACTIVITY

This Table Shows Volume in c.c. (A) of the Various Specimens; Peptic Activity Expressed as Mg. Edestin Digested per c.c. of Gastric Juice, (B); and Total Peptic Activity as Obtained by Multiplying the Former Two, (A × B)

Case	Diagnosis	Volume (A)			Mg. Edestin digested per c.c. gastric juice (B)			Total Peptic Activity (A × B)		
		F	H	P	F	H	P	F	H	P
5	Normal	13	195	21	331.7	509.	482.2	4312.1	99255.	10126.2
6	Normal	44	85	52	220.9	521.4	435.7	9719.6	44319.0	22656.4
7	Normal*	22	21	130	537.	920.8	477.	11814.	19336.8	62010.0
8	Normal*	50	116	200	181.	376.5	296.3	9050.	43674.	59260.0
3	Pernicious anemia	7	2.5	19	127.1	117.2	313.9	889.7	293.0	3426.1
4	Pernicious anemia	0	7	6	—	464.9	298.6	—	3266.2	1791.6
9	Pernicious anemia	24	31	21	—	—	—	—	—	—
10	Pernicious anemia*	16	21	21	17.6	98.6	33.1	281.6	2070.6	695.1
2	Duodenal ulcer	33	72	35	298.2	533.1	658.9	9840.6	35172.0	19944.2
11	Duodenal ulcer	20	81	120	565.6	860.3	516.7	11312.	69684.3	62004.3
12	Cancer of stomach*	6	76	170	61.	13.0	4.0	492.	988.0	680.
1	Functional disease	15	55	19	353.3	332.9	359.8	5299.5	18309.5	6836.2
13	Functional disease*	110	45	110	479.3	846.1	924.5	52723.	38074.5	101695.0

* Pilocarpine given first.
F = Fasting,
H = After histamine,
P = After pilocarpine.

Analysis of Results

Volume. In the four normal cases, whichever drug was used for the first hour's stimulation produced a very definitely greater volume. In one instance this ratio was greater than 9:1. With the four cases of pernicious anemia, the volume was approximately the same for both drugs regardless of which was studied first. There was one exception, in which the quantities were small, but in which the second drug given (pilocarpine in this instance) produced a greater volume of juice. In the two cases of duodenal ulcer, one responded better to histamine and one better to pilocarpine though both patients received histamine first. In the other cases as in the normals, the first stimulant gave the best response. When all cases were considered it was apparent that pilocarpine stimulation produced a greater volume than histamine stimulation.

Free and Total Acid. There was very little difference in the concentration of acid when the results during the two periods of stimulation were compared, regardless of which drug was given first. Only in one normal subject was there a definite response favoring histamine.

Total Chlorides. The greater concentration of chlorides practically always occurred with the smaller volume, regardless of which drug was used for stimulation.

Pepsin. In the normal subjects the greatest peptic activity per c.c. always followed histamine stimulation regardless of which drug was given first. When the total peptic activity (volume of spec. in c.c. x peptic activity per c.c. expressed as mg. Edestin digested) was considered, the greatest values were found following the drug which was used as the first stimulant. This also corresponded with the greater volume of secretion. In these cases the peptic activity per c.c. following histamine was always greater than the fasting value. The figures following pilocarpine were also definitely greater than the fasting values with one exception, in which instance a very large volume of juice was secreted after pilocarpine stimulation.

In the four cases of pernicious anemia which were studied, one patient gave no evidence of pepsin secretion, one responded better to pilocarpine and two better to histamine. In each of the last three cases the histamine was given first. These values expressing peptic activity were also definitely higher than the fasting values. The figures for total peptic activity were comparable with those for peptic activity per c.c.

One ulcer patient had greater evidence of peptic activity per c.c. following pilocarpine while the other had a higher value following histamine. The total peptic activity was higher in each case following histamine; however, it was the first drug administered in both instances.

In the one case of carcinoma of the stomach, the peptic activity per c.c. was higher in the fasting specimen than in those following histamine and pilocarpine stimulation. The peptic activity per c.c. and the total peptic activity were greater following histamine stimulation than after pilocarpine,

though the latter was given first and the volume of pilocarpine secretion was more than twice as great.

There was no marked difference in peptic activity per c.c. in the functional cases following histamine and pilocarpine though when total activity was considered the higher values were associated with the larger volumes.

Discussion

The effect of pilocarpine on the gastric secretion has been previously studied on numerous occasions, though we are aware of no previous study on humans taking into account quantitatively the various elements of the gastric juice. Moreover, the results obtained by the various investigators have not been comparable. The preponderance of opinion seems to have been that pilocarpine caused no increase and perhaps depressed the gastric acidity. Altshuler [7] in 1928 reviewed the previous work, and reported some original studies but determined only the free and total acidity on humans. He also studied the effects of atropine and epinephrine on the gastric secretion. Schwab [8] and Mitrovitch [9] independently concluded that a decrease in acidity resulted following the use of pilocarpine. The former was of the opinion that this effect was not due to an increased secretion of gastric mucus and the latter felt that the action of pilocarpine was very similar to that of atropine in inhibiting the gastric secretion.

Vineberg and Babkin [10] in 1931 suggested the use of pilocarpine with histamine as a test of gastric function on the basis of their experimental work with dogs. They concluded that histamine stimulated the secretion of water, hydrochloric acid and other inorganic constituents without affecting enzyme action. Pilocarpine on the other hand tended to stimulate the secretion of enzymes. Because of these findings they pointed out that a "combination of histamine and pilocarpine produces a synthetic gastric juice approaching normal."

Gilman and Cowgill [11] also maintained that histamine did not stimulate the secretion of pepsin; their work also was done on dogs.

Polland [3] on the other hand concluded that histamine did stimulate the secretion of pepsin.

It has been shown by Engelbach and Brown [1] that the gastric secretion in its response to histamine is not constant from day to day. For this reason it was thought that a better comparison between the actions of histamine and pilocarpine could be made if successive hourly periods were studied. While this method does not seem to give perfectly comparable results, as the response during the second hour in some cases apparently was diminished, it seems that some very definite information was obtained.

It is evident from the tables that the greater total peptic activity does not necessarily occur in the specimen where the greater peptic concentration is obtained. (See Cases 7, 8, 2, 1). The digestive power of gastric juice under standard, optimal conditions is dependent upon the amount of pepsin

present. Because of these facts we feel that a better quantitative index of peptic activity can be obtained if the volume of gastric secretion during a given period is considered.

Summary

It has been demonstrated that pilocarpine is a true stimulant of gastric secretion, its chief effect being an increased volume of gastric juice; the acid and pepsin secretions, however, are also stimulated. Histamine also stimulates the secretion of pepsin, and the values obtained are not explained by a process of washing out of the gastric crypts as suggested by some workers.

No definite evidence is obtained to support the opinion expressed by some experimenters that pilocarpine is a better stimulant of enzyme secretion than histamine. The results are not sufficiently conclusive to say that either is a better stimulant for enzyme secretion than the other. This also seems to be true in regard to the secretion of acid. There is no appreciable difference in the effect of these two drugs on the secretion of total chlorides.

No untoward symptoms were noted from the use of pilocarpine in the doses given, with the exception of slight nausea which was experienced by one patient. A definite increase in salivation was noted in practically all cases.

The estimation of total peptic activity during a given period would seem to be a better quantitative index of peptic secretion than a determination of the concentration of pepsin.

Conclusions

1. Pilocarpine is a stimulant of gastric secretion, as shown by its effect on the volume, acidity, chlorides and pepsin content of the gastric juice.
2. Histamine stimulates the secretion of pepsin.
3. No evidence is obtained that pilocarpine is more effective in the stimulation of pepsin secretion than is histamine.
4. Histamine has not been proved to be a definitely better stimulant of gastric secretion than pilocarpine as determined by the volume, acidity, total chlorides and pepsin content of the gastric juice.

BIBLIOGRAPHY

1. Engelbach, F., and Brown, C. L.: Variations in the volume and in the acid content of gastric secretion of normal individuals following stimulation by histamine, Ann. Int. Med., 1933, vi, 1560–1564.
2. Sievers, E. F., and Cook, J. E.: Competency of Rehfuss tube as complete evacuator, Jr. Lab. and Clin. Med., 1932, xvii, 1120–1123.
3. Polland, W. S.: Stimulation of gastric pepsin by histamine, Jr. Clin. Invest., 1932, xi, 449–454.
4. Polland, W. S.: Effect of atropine upon gastric secretion after histamine stimulation, Jr. Clin. Invest., 1930, ix, 319–332.
5. Van Slyke, D. D.: Determination of chlorides in blood and tissues, Jr. Biol. Chem., 1923, lviii, 523–529.

6. POLLAND, W. S., and BLOOMFIELD, A. L.: Quantitative method for estimation of pepsin, Jr. Clin. Invest., 1929, vii, 45–55.
7. ALTSHULER, A. M.: Gastric secretion; its alteration by use of atropine, epinephrine and pilocarpine, Arch. Int. Med., 1928, xlii, 117–134.
8. SCHWAB, E.: Die Wirkung einzelner Arzneimittel auf die Magenfunktionunter gleichzeitiger Berücksichtigung von Blutdruck, Puls und Blutbild; Pilocarpinwirkung, Ztschr. f. d. ges. exper. Med., 1928, lxiii, 163–180.
9. MITROVITCH: Action of pilocarpine on the stomach, Comp. rend. Soc. d. biol.; Abstr., Jr. Am. Med. Assoc., 1926, lxxxvi, 1402.
10. VINEBERG, A. M., and BABKIN, B. P.: Histamine and pilocarpine in relation to the gastric secretion, Am. Jr. Physiol., 1931, xcvii, 69–73.
11. GILMAN, A., and COWGILL, G. R.: Effect of histamine upon secretion of gastric pepsin, Am. Jr. Physiol., 1931, xcvii, 124–130.

THE INCIDENCE AND SIGNIFICANCE OF THE SICKLE CELL TRAIT *

By L. W. Diggs, M.D., C. F. Ahmann, Ph.D., and Juanita Bibb, A.B.,
Memphis, Tennessee

If one takes a drop of blood from each member of an unselected series of negroes, seals the drops under cover-slips, and examines them microscopically over a period of hours, he observes striking curved and pointed distortions of the erythrocytes in an appreciable number of the preparations. (Figure 1.) Erythrocytes assuming such bizarre stellate shapes are called "sickled cells" and individuals whose erythrocytes are capable of undergoing such a metamorphosis under suitable conditions are said to possess the "sickle cell trait." The anomaly is hereditary and is thought to be transmitted as a dominant Mendelian characteristic. Within the large group of those who inherit the sickle cell trait, an undetermined number, due to factors unknown, develop varying degrees of "sickle cell anemia," a hemolytic type of blood dyscrasia with characteristic clinical and pathological features.

Estimations of the frequency of occurrence of the sickle cell trait have been recorded by a number of observers, but the number of individuals examined has been relatively few; most of the studies have been made on hospital patients, and little attention has been given to the variable factors which play a part in the detection of the anomaly. The clinical importance of the sickle cell trait in absence of anemia, and the relationship of the trait to sickle cell anemia are subjects of controversy. For these reasons, it seems justifiable to present evidence revealed in our investigations which deals with the incidence and significance of the sickle cell trait.

Method

The individuals included in the surveys reported in this article were taken at random from groups of normal and hospital negroes and white people. One series examined by Ahmann consisted of negro school children and teachers in the grammar and high schools of Gainesville, Florida. Another series consisted of hospital negroes in the medical, surgical, obstetrical and pediatric wards, and in the out-patient clinic of the Memphis General Hospital, and in the medical wards of the Shelby County Hospital, Memphis, Tennessee. The white subjects examined for the presence of the sickle cell trait were medical students of the University of Tennessee and medical patients of the Memphis General Hospital.

Sealed moist preparations, used throughout the study as a means of detection of the sickle cell anomaly, were made in the following manner.

* Received for publication March 31, 1933.
From the Department of Clinical Pathology, University of Tennessee, Pathological Institute, Memphis, Tennessee, and from the Nutritional Division of the Experimental Station, University of Florida, Gainesville, Florida.

In the school series, new slides and new No. 0 and No. 1 cover-slips were boiled in cleaning solution, rinsed in distilled water and 95 per cent alcohol; then left in a mixture of alcohol and ether until dried for use. In the hospital series new slides and new No. 1 and No. 2 cover-slips were used. The method of cleaning varied; most of the glassware, however, was washed for 24 hours in running tap water and placed in 95 per cent alcohol, until dried for use. Capillary blood from alcohol cleaned fingers or heels was used for

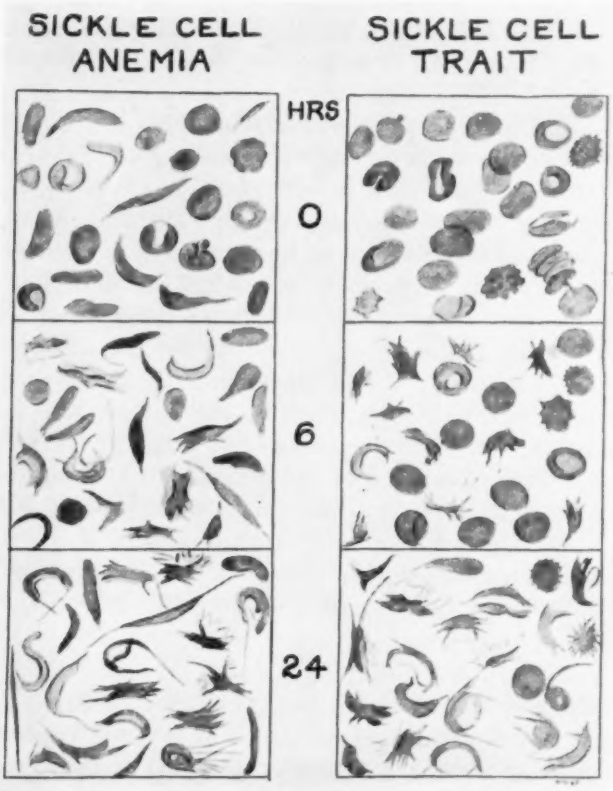


FIG. 1. Drawing showing the morphology of sickled erythrocytes in sickle cell anemia and in the sickle cell trait as revealed in sealed moist preparations at the time of making the preparations and after six hours and after 24 hours.

all preparations with the exception of those made in the out-patient department, where venous blood drawn for routine Wassermann tests was utilized. A small drop of blood was taken on a cover-slip, and the cover-glass placed drop-side down on a slide. The blood was allowed to spread without pressure, after which the edges of the cover-glass were rimmed with petrolatum. In the first 500 cases only one moist preparation was made per patient, but in the remaining hospital cases and in all of the school cases, two preparations per patient were made. The sealed drops were left at room temperature

and examined under high dry magnification four times, once immediately after returning to the laboratory, and at 24 hour intervals thereafter for three days. The sickle cell trait for a given individual was recorded as positive when definite long tapering filaments and typical sickle cell distortions were observed. Crenated cells, elliptical cells, cells with blunt filaments and poikilocytosis of a questionable and non-specific nature were not considered as manifestations of the sickle cell phenomenon.

Results

The number of negroes examined in the hospital series was 2,539, of which number 211 or 8.3 per cent were demonstrated to have sickled cells in moist preparations. Of 674 negro school children and teachers examined, the sickle cell phenomenon was observed in 65 or in 9.6 per cent of the preparations. By combining our series with those previously recorded in the literature,[1-11] the average frequency of demonstration of the trait in negroes is found to be 7.3 per cent (619 in 8,453). (Table 1.) It is probable that the real incidence of the sickle cell trait is higher than this demonstrated average, because most of the sources of error in the method are on the side of not detecting the trait when it is present rather than in making false positive diagnoses.

Moist preparations were made with the blood of 309 white people and in no preparation was there any evidence of sickle cell distortion. Other sur-

Table I

Incidence of the Sickle Cell Trait

Author	Place	Number Examined	Number with Trait	Per cent with Trait
Negroes				
Sydenstricker, Mulherin and Houseal	Ga.	300	13	4.3
Cooley and Lee	Mich.	400	30	7.5
Miyamoto and Korb	Mo.	300	19	6.3
Wollstein and Kreidel	N. Y.	150	13	8.6
Josephs	Md.	250	16	6.4
Smith	La.	100	5	5.0
Dolgopol and Stitt	N. Y.	77	4	5.2
Levy	N. Y.	213	12	5.6
Graham and McCarty	Ala.	1,500	122	8.1
Brandau	Tex.	150	10	6.7
Sydenstricker	Ga.	1,800	99	5.5
Diggs, Ahmann and Bibb	Tenn.	2,539	211	8.3
Ahmann	Fla.	674	65	9.6
Total		8,453	619	7.3
Whites				
Sydenstricker	Ga.	1,000	0	0.0
Miyamoto and Korb	Mo.	100	0	0.0
Diggs, Ahmann and Bibb	Tenn.	309	0	0.0
Total		1,409	0	0.0

veys of white people have likewise yielded negative results.[3, 12] (Table 1.) The series reported by Lawrence,[13] which is falsely interpreted by some as being a proved demonstration of sickled erythrocytes in white people, is not included, for he describes and pictures elliptical cells and not true sickled cells. Wollstein and Kreidel [4] were unable to demonstrate the sickle cell phenomenon in white children, but fail to state the number examined.

Isolated instances of the sickle cell trait in white people have been placed on record by Castana,[14] Archibald,[15] Stewart,[16] Cooley and Lee,[17] Sights and Simon,[18] and by Rosenfeld and Pincus.[19] There is reason to suspect negro blood in the cases reported by Archibald and by Stewart. The claims of Castana and of Sights and Simon are contestable because of inadequate investigation of the families and because they did not prove conclusively by word description or illustration that they were dealing with the sickle cell trait. Cooley and Lee presented evidence of the sickle cell phenomenon in a Greek family, and Rosenfeld and Pincus demonstrated the presence of sickled cells in an Italian family. In both of these families there was no evidence of mixed blood. From these observations it is evident that the sickle cell trait is frequent in the negro race and quite rare in the white race, and that clearly established cases among white people have been limited to those of Mediterranean stock. If the sickle cell trait is a dominant characteristic, there will come from the interbreeding of the races an increasing number of cases with the sickle cell trait in those apparently white.[19] Whether or not the trait occurs in pure white strains will long remain a disputed point, and will be settled by preponderance of evidence rather than by single cases.

Examination of table 1 reveals slight differences in the incidence of the sickle cell trait as recorded by different observers, which is to be expected in any frequency estimation which deals with relatively small series and with many variable factors. Climate and geographical location do not seem to be important factors, as there are no significant or constant variations in the incidence in the widely separated localities where surveys have been conducted.

An analysis of the incidence according to sex discloses an even distribution of the sickle cell trait in males (8.4 per cent) and in females (8.1 per cent). (Table 2.)

An examination of the series to determine the incidence of the sickle cell trait according to age reveals the following findings. The lowest percentage occurred in new born babies, the sickle cell trait being demonstrated in only 3.1 per cent (6 in 159). It was also noted that the sickle cell distortion in this group was less marked and developed more slowly than in adults with the trait. In the negro school children the sickle cell phenomenon was demonstrated in 8.6 per cent (24 in 270) of those from 6 to 10 years of age, in 9.7 per cent (27 in 277) of those 11 to 15 years of age, and in 11.2 per cent (13 in 115) of the 16 to 20 year old group. This slight increase in incidence with advancing years is probably not significant. The

TABLE II

Incidence of the Sickle Cell Trait According to Sex

Author	Number Examined	Number with Trait	Percentage
Females			
Miyamoto and Korb	196	14	7.1
Graham and McCarty	944	72	7.7
Diggs, Ahmann and Bibb	1,297	106	8.2
Ahmann	394	38	9.7
Total	2,831	230	8.1
Males			
Miyamoto and Korb	104	5	4.8
Graham and McCarty	556	50	8.7
Brandau	150	10	6.6
Diggs, Ahmann and Bibb	1,162	97	8.3
Ahmann	280	27	9.6
Total	2,252	189	8.4

frequency of demonstration of the sickle cell trait according to age for the entire group of negroes examined, including both the hospital and school series, is given in figure 2.

The youngest negro found to have sickled erythrocytes was a premature infant, and the oldest was 99 years of age. Twelve negroes who remembered incidents of slave days and the Civil War were still with us in spite of the sickle cell trait, which is rather definite evidence that the anomaly is compatible with life even beyond the period of life expectancy. These observations are not consistent enough to lead to very definite conclusions, but they suggest that the trait is least demonstrable in moist preparations in the newly born, most frequently observed in childhood and tends to decrease slightly with advancing years.

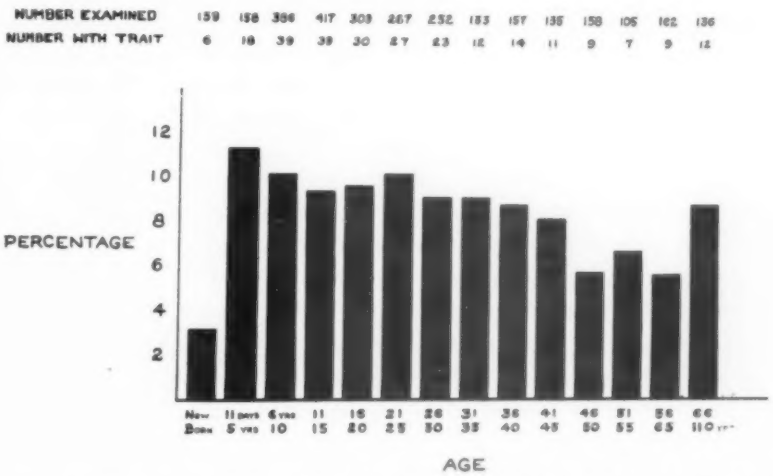


FIG. 2. The incidence of demonstration of the sickle cell trait in negroes according to age.

An evaluation of the effect of the mixture of white and negro blood on the incidence of the sickle cell trait was attempted by noting the frequency of occurrence of the trait in light and very light negroes as contrasted with dark and black types. It was found that 13.1 per cent (27 in 206) of the lightly pigmented negroes possessed the trait, whereas the percentage incidence in a comparable series of the deeply pigmented negroes was 7.1 per cent (51 in 701). The finding of an apparently significantly higher incidence in negroes with mixed blood than in pure negroid types must be confirmed before we speculate as to its cause, but it suggests avenues for further investigation.

In order to determine the effect of the state of health on the incidence of the sickle cell trait, comparisons were made of the frequency of occurrence of the trait in healthy negro school children and in hospital children of the same age. It was found that the incidence in the school series was 9.7 per cent (64 in 662) and in the hospital series the incidence was 9.8 per cent (44 in 450). These two series are not entirely comparable in that the examinations were made in different localities and the technic used was not exactly the same. Sydenstricker [11] demonstrated the sickling trait in 5.5 per cent of 1,800 presumably healthy negro children in the public schools, and Brandau [10] found that 6.7 per cent of 150 negro applicants for industrial work possessed the sickle cell trait. These figures are within the range of variation of similar series reported on hospital patients. From these findings we may conclude that a higher incidence of the sickle cell trait among sick negroes than among the healthy remains to be proved.

That the method of collection of blood may have an effect on the demonstrability of sickled cells is suggested by the fact that in a series of 823 preparations made with venous blood, sickled cells were observed in 10.2 per cent while in 1,716 preparations made with capillary blood the incidence was 7.4 per cent. It was found that the weight of the cover-slip was not a factor of importance in the determination of the sickle cell trait. Series of preparations made on the same patients, using No. 1 and No. 2 cover-slips, revealed a slower and a less complete development of the sickling phenomenon under the heavier cover-slip within the first few hours, but at 24 hours there was no consistent difference.

The Significance of the Sickle Cell Trait

A review of the literature dealing with the significance of the sickle cell trait shows that early workers [20, 21] considered the demonstration of sickled cells to be of definite clinical importance, but with increasing knowledge the general trend of opinion has been to assign to the sickle cell trait less and less significance. It is now generally conceded that the diagnosis of the sickle cell trait in absence of anemia can only be made by use of special methods such as the moist preparation or gas chamber, and that the history, physical signs and ordinary laboratory procedures do not give information which can be relied upon for recognition.[9, 10, 22, 23] Although many opinions have been

expressed as to the significance of the sickle cell trait, there are few facts and figures. Observations made in our studies may elucidate certain disputed points.

Greenish-yellow discoloration of the sclerae is a common finding in patients with sickle cell anemia and is thought by some to be also characteristic of the sickle cell trait. The sclerae were examined in 438 negroes in our series on whom moist preparations were made. It was found to be extremely difficult accurately to describe the combinations of pigmentary change encountered. The sclerae of many individuals had background colors of gray, slate and brown, which were further complicated by black and brown macules, by dilatation of superficial vessels giving red appearances and by pingueculae. The sickle cell phenomenon was demonstrated in 28 and absent in 313 negroes who were considered to have scleral tints of green and of yellow. In 97 negroes with no definite discoloration, six were found to have sickled cells. From these investigations we come to the definite conclusion that the color of the sclerae in negroes cannot be used as a diagnostic aid in the detection of the sickle cell trait.

In order to determine whether patients with the sickle cell trait had leg ulcers more commonly than did those without the trait, the legs of 304 negroes were examined at the time moist preparations were made. It was noted that many negroes had scars and pigmentary changes of some kind on their legs, most of which could be accounted for by the trauma of barefoot years, industrial pursuits and superficial burns from huddling around fireplaces and red hot stoves. Only those cases with definite rounded scars who gave a history of delayed healing were recorded as positive. No open lesions were found. Of 258 negroes with no scars of the type found in sickle cell anemia, 21 (8.1 per cent) possessed the sickle cell trait, whereas within the group of 46 negroes with suspicious scars there were four negroes (8.7 per cent) in whom sickled cells were demonstrated. Although this series is too small and the criteria for judging the ulcerations too indefinite to draw conclusions, it does not support the idea that leg ulcers occur more commonly in those with the sickle cell trait than in normal individuals.

It has been generally assumed that negroes with the sickle cell trait have a tendency to develop anemia, but there is little evidence to support this idea, beyond the fact that a few have sickle cell anemia. Cooley and Lee [2] stated that "moderate anemia seems to be the rule among our colored children, and that there is practically no difference in this regard between those with and without sickled cells." Miyamoto and Korb [3] came to the same conclusion. Josephs [5] found no anemia in 16 children with characteristic sickle cell changes. In order to determine in a normal group whether or not those with the sickle cell trait were more anemic than those without the trait, hemoglobin determinations by the Dare method were made on 672 negro school children. Of 65 cases found to have the sickle cell trait, the highest hemoglobin reading was 103 per cent, the lowest 60 per cent and the average for the group 82.6 per cent. In the series of 607 without the trait, the

highest hemoglobin was 108 per cent, the lowest 60 per cent and the average 81.4 per cent. Frequency distribution curves in percentage are given in graphic form. (Figure 3.) These findings indicate that the majority of individuals with the sickle cell trait are no more anemic than others in the same environment without the trait.

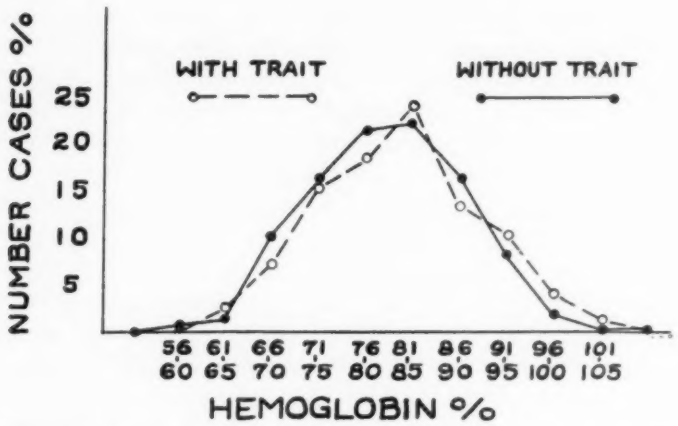


FIG. 3. Frequency distribution curve of hemoglobin determinations in 65 negro school children with the sickle cell trait and in 607 negro school children without the trait.

It is not as yet possible to estimate with any degree of accuracy how often sickle cell anemia develops within the group of those whose erythrocytes sickle. Severe cases of sickle cell anemia with characteristic symptoms and signs often are not recognized, and mild cases with less definite diagnostic signs are seldom detected. Sydenstricker [20] estimated that in hospital patients the ratio of anemia to the trait was one to nine. In a recent survey of school children, he found the ratio to be 1 to 50 and adds that "among children admitted to the hospitals and out-patient clinics the number is of course greater." On the medical and pediatric wards of the Memphis General Hospital during a 30 month period 14 cases of sickle cell anemia were recognized. Estimating the number of patients with the sickle cell trait as 7.4 per cent of the total number of admissions during the same period, the ratio of sickle cell anemia to the sickle cell trait is 1 to 40. These figures are merely rough estimates, but if approximately correct they indicate that sickle cell anemia is much more frequent than is commonly believed and that the number affected in the United States alone probably numbers in the tens of thousands.

SUMMARY AND CONCLUSIONS

1. The sickle cell trait was demonstrated by means of sealed moist preparations of whole blood in 8.3 per cent of 2,539 out-patient and hospital negroes examined at Memphis, Tennessee, and in 9.6 per cent of 674 negro school children and teachers at Gainesville, Florida.

2. The incidence of the sickle cell trait as demonstrated in moist preparations in the combined surveys reported in the literature and including the series reported in this paper is 7.3 per cent (619 in 8,453 examined).

3. The sickle cell trait has not been demonstrated in recorded surveys of white people, and the only reasonably proved instances of the sickle cell trait in families with unmixed blood have been limited to those of the Mediterranean stock.

4. Geographical location, sex and state of health do not appear to be factors affecting the incidence of the sickle cell trait.

5. In our series the frequency of demonstration of the sickle cell trait varied with age, degree of pigment and method of collection of blood, but the series are too small and the uncontrolled factors too numerous to draw definite conclusions.

6. That the sickle cell trait in absence of anemia is of little clinical significance is supported by the following observations:

(*a*) The trait is compatible with long life.

(*b*) The incidence in hospital cases has not been proved to be higher than in healthy individuals.

(*c*) Leg ulcers and greenish-yellow discoloration of the sclerae appear as frequently in those without the trait as in those with the trait.

(*d*) Hemoglobin determinations in a series of negro school children revealed parallel findings in those with and without the trait.

7. The ratio of sickle cell anemia to the sickle cell trait is estimated 1 to 40.

8. The importance of the sickle cell trait appears to be limited to the relatively small group who in addition to the trait have sickle cell anemia.

BIBLIOGRAPHY

1. Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W.: Sickle cell anemia, report of two cases in children, with necropsy in one case, Am. Jr. Dis. Child., 1923, xxvi, 132–156.
2. Cooley, T. B., and Lee, P.: Sickle cell phenomenon, Am. Jr. Dis. Child., 1926, xxxii, 334–340.
3. Miyamoto, K., and Korb, J. H.: Meniscocytosis (latent sickle cell anemia); its incidence in St. Louis, South. Med. Jr., 1927, xx, 912–916.
4. Wollstein, M., and Kreidel, K. V.: Sickle cell anemia, Am. Jr. Dis. Child., 1928, xxxvi, 998–1011.
5. Josephs, H.: Clinical aspects of sickle cell anemia, Bull. Johns Hopkins Hosp., 1928, xliii, 397–398.
6. Smith, J. H., Jr.: Sickle cell anemia, Med. Clin. N. Am., 1928, xi, 1171–1190.
7. Dolgopol, V. B., and Stitt, R. H.: Sickle cell phenomenon in tuberculosis patients, Am. Rev. Tuberc., 1929, xix, 454–460.
8. Levy, J.: Sicklemia, Ann. Int. Med., 1929, iii, 47–54.
9. Graham, G. S., and McCarty, S. H.: Sickle cell (meniscocytic) anemia, South. Med. Jr., 1930, xxiii, 598–607.
10. Brandau, G. M.: Incidence of sickle cell trait in industrial workers, Am. Jr. Med. Sci., 1930, clxxx, 813–817.
11. Sydenstricker, V. P.: Discussion of paper, South. Med. Jr., 1932, xxv, 620.

12. Sydenstricker, V. P.: Sickle cell anemia, South. Med. Jr., 1924, xvii, 177–183.
13. Lawrence, J. S.: Elliptical and sickle-shaped erythrocytes in the circulating blood of white persons, Jr. Clin. Invest., 1927, v, 31–49.
14. Castana, V.: I Gigantociti e le Anemie Semilunari, Pediatria, 1925, xxxiii, 431–440.
15. Archibald, R. G.: Sickle cell anemia in the Sudan, Tr. Roy. Soc. Trop. Med. and Hyg., 1926, xix, 389–393.
16. Stewart, W. B.: Sickle cell anemia; report of case with splenectomy, Am. Jr. Dis. Child., 1927, xxxiv, 72–80.
17. Cooley, T. B., and Lee, P.: Sickle cell anemia in a Greek family, Am. Jr. Dis. Child., 1929, xxxviii, 103–106.
18. Sights, W. P., and Simon, S. D.: Marked erythrocytic sickling in a white adult associated with anemia, syphilis and malaria; report of case, Jr. Med., 1931, xii, 177–178.
19. Rosenfeld, S., and Pincus, J. B.: Occurrence of sicklemia in white race, Am. Jr. Med. Sci., clxxxiv, 674–682.
20. Sydenstricker, V. P.: Further observations on sickle cell anemia, Jr. Am. Med. Assoc., 1924, lxxxiii, 12–17.
21. Graham, G. S., and McCarty, S. H.: Sickle cell anemia, Jr. Lab. and Clin. Med., 1927, xii, 536–547.
22. Steinberg, B.: Sickle cell anemia, Arch. Path., 1930, ix, 876–897.
23. Anderson, W. W., and Ware, R. L.: Sickle cell anemia, Jr. Am. Med. Assoc., 1932, xcix, 902–905.

HEART BLOCK IN THE YOUNG*

By I. I. LEMANN, M.D., F.A.C.P., *New Orleans, Louisiana*

IT IS GENERALLY thought that heart block occurs exclusively in persons past middle age, chiefly in those of old age. A review of the literature of the past six years will soon yield a very different impression. I have been able to find in the literature reports of 99 cases of atrioventricular block occurring in patients below the age of 30. There are, in addition to these, several other titles in the literature to which I have not had access, or concerning which I am not certain. The probable number reported is, therefore, approximately 100. In five the diagnosis was made on clinical evidence only; in all the rest it was substantiated by electrocardiographic tracings or phlebograms. Some idea of the incidence of heart block in general, and in young people under 30 years of age, may be formed from the following: Paul White [1] states that, "in an electrocardiographic series of 9000 patients with cardiac symptoms or signs, atrioventricular block was diagnosed in 581 cases (6.5 per cent). Coronary disease was apparently responsible in 35 of another series of 69 cases of atrioventricular block (29.3 per cent), rheumatic infection in 19 (32.2 per cent), congenital defect in one, luetic involvement in one, digitalis medication in nine, and an unknown factor in four cases." In an electrocardiographic series of 3000 patients in Touro Infirmary we have had 38 cases of atrioventricular block, (11 complete block, 6 partial block, 21 delayed conduction time beyond 0.20 seconds). One of the complete blocks and one of the partial blocks were in patients aged 22 and 28, respectively. By courtesy of Dr. Richard Ashman I am permitted to quote the statistics of Charity Hospital, New Orleans: In 2825 patients with cardiac symptoms or signs, there were 264 patients with affections of the A–V conduction system. Of these 264 patients, 14 had complete block and of these one was 22 years old; 16 had a partial block and of these two were 24 and 29 years old, respectively. There were 23 other patients below the age of 30 with an A–V conduction time of 0.20 seconds, or more. Included in these last 23 patients were patients acutely ill with rheumatic fever and diphtheria, patients with rheumatic and luetic heart disease as well as patients with no definite heart disease. Delayed conduction time due to digitalis was not included in the series of 23 young patients, but was included in the total collection of 264 patients of all ages. It becomes apparent, therefore, that heart block in the young is not an extreme rarity but rather constitutes an important portion of the total incidence of heart block. Instances of heart block in children and young people are for the most part recorded in scattered and single reports. Archigène [2] collected 39 cases. This collection and those of Yater [3] (30 cases of congenital heart

* Read before the Association of American Physicians, Washington, D. C., May 9, 1933. Received for publication June 7, 1933.

From the Department of Medicine, School of Medicine, Tulane University, and The Medical Service, Touro Infirmary.

block), Wood and Rogers [4] (six cases of congenital heart block), and the personal series of Sprague and White [5] (11 cases of juvenile block), are the most important. Their bibliographies serve as the chief guides to the literature.

The frequency with which heart block occurs in the young is not the only astonishing feature. Equally surprising is the lack of serious symptoms in many patients and the ability of these patients to carry on the most strenuous lives. In many of them the bradycardia was the only finding of note, and even this was discovered in some instances accidentally at routine examination. The patient of de Massary and Lian,[6] who had had a bradycardia from his earliest years, engaged in the most violent sports (horse racing, fencing and automobile racing) and had never suffered the slightest inconvenience until his thirty-third year when he began to have syncopal attacks. Others have gone through operations and severe illnesses such as pneumonia and whooping cough, as well as the childhood exanthems. There are on record six well authenticated cases of young women with heart block who have gone through pregnancy and confinement without difficulty, and apparently without any subsequent damage.[7] Stokes-Adams syndrome was present in only a minority of the 99 cases. Clerc [8] estimated its incidence as 30 per cent in the series gathered by his pupil Archigène.[2] It did not seem to be more frequent in complete block than in partial block.

The prognosis is thus much less serious than would have been anticipated. In many, in fact in most, of the cases referred to in this collection of approximately 100 the block was permanent, and the block was known to exist through many years. It is to these lasting blocks that I desire to call your attention rather than to the evanescent blocks incident to infectious disease, though in passing it may be stated that these latter probably occur more frequently than is usually thought. The patient of de Massary and Lian [6] to whom reference has already been made, had a bradycardia at birth. His syncopes began and the heart block was proved when he was 34. He was still living 10 years later. The bradycardia of Calandre's [9] patient also dated from birth; the heart block was proved at the age of 21, when the patient still had no symptoms. Zander's [10] child, who was seven in 1912 when the diagnosis was established, was seen again in 1925, 13 years later, when he had no complaint. Two cases are recorded in the literature, that are not included in the group of 99 but that are worth recording in this connection. Taussig's [11] patient of 70 knew, according to her family, that she had had since birth a slow pulse, accompanied by nervous crises. She had borne children. Jacquier's [12] patient of 78 had a slow pulse, noted in the first days of his life, remarked upon by his doctor at that time, and the bradycardia continued throughout his life. At 78 his pulse was 26 on awakening, 32 after he walked a few minutes, or climbed the stairs. He had never had syncope or vertigo. While it is true that absolute proof of heart block throughout these long lives is lacking, the presumptive evidence is extremely strong. Willius [13] observed the course of his patient from 41 to 57 years

of age. She had known of the bradycardia since the age of 36, and presumably it dated to diphtheria at 31. She had had no syncope nor any symptoms related to the heart. Hyman's [14] patient, who was shown to have a complete block at 57, had known of his slow pulse since the age of 12, and could always get sick leave from school by having his pulse counted. He had worked in all corners of the world under arduous physical and mental conditions. At 57 he had no syncope, and his physical examination revealed nothing of importance other than heart block. While in general, young patients with heart block often live normal lives, still it must be recorded that they are liable to sudden death. Aldrich's [15] patient died on entering the water to swim, although she had previously swum frequently.

We must, of course, in these young patients look for causes of heart block entirely different from those found in the aged; in the latter, arteriosclerosis, coronary disease, and myocardial fibrosis constitute the chief basis. White [5] considers the following classes of heart block in the young from an etiological standpoint: (1) acute infections; (2) rheumatism; (3) congenital abnormalities; (4) trauma; and (5) idiopathic; he has himself reported examples from each class. Of the acute infections he places diphtheria foremost, an opinion concurred in by Clerc.[8] White [5] writes, however: "When dissociation of the auricles and ventricles arises in the course of acute diphtheria, the patient is critically ill, and in the great majority of cases does not live long. It still remains to be demonstrated conclusively that diphtheria is the agent responsible for heart block lasting more than a few days. A study we have recently made of 100 patients following severe diphtheria, has revealed no persistent heart lesion." Butler and Levine,[16] on the other hand, after studying a group of 20 patients with proved heart block without the customary causes, such as coronary heart disease, digitalis, fever, and rheumatic infections, and finding in 50 per cent a history of diphtheria in childhood, in contrast with a history of diphtheria in only 6 per cent of 600 consecutive controlled surgical cases, came to the conclusion that "diphtheria in childhood appears to be an etiological factor in the development of heart block in later years." At any rate diphtheria looms large in the histories, and in some cases a block dates back to the diphtheria.[5] Various other infections have been incriminated because of the heart block developed in their course. Influenza has been definitely so connected, as has typhoid. Most important, of course, is the rôle played by rheumatism. The block may be temporary or permanent.

Heart block was congenital in 42 of the approximately 100 published cases. This chapter of congenital heart block has in recent years dominated the picture of juvenile block in the literature. Yater [3] in 1928 gathered 29 cases (some are included in Archigène's [2] series), and added one of his own. Wood and Rogers [4] in 1932 added six more cases from the literature with one of their own. To this total of 37 I now add three more from the recent literature (Sprague and White,[5] Švejcar and Francová-Helbichova,[17] and Godfrey and Palmer,[18] as well as two more from Archigène's series (de

Massary and Lian, and Calandre)), which seem to me to deserve to be considered congenital. This makes a total of 42 cases of congenital heart block.

Congenital heart block is apparently related to congenital anomalies for evidence was usually present in the reported cases warranting the diagnosis of these latter. Chief among these anomalies was the presence of a defect in the interventricular wall, giving rise to a loud systolic murmur heard over the whole precordium, to cyanosis and to club fingers. Carter and Howland [19] have pointed out that an abnormal fetal development of the ventricular cavities and the interventricular septum may involve a group of cells later to become the A–V node and the upper part of the main stem of the conducting system. Indeed, as these authors state, in view of the definite relationship between the main trunk of the conduction system and the interventricular foramen, it is interesting that more frequent disturbance of the conduction system is not met with when anomalies of the septum are present. Unfortunately only four [20] autopsies have been reported on patients with congenital heart block. All of these showed septal defects. Other abnormalities suspected, but not proved, were aorto-pulmonary patency, pulmonary artery stenosis, and pulmonary valve stenosis. It has been suggested by Yater [3] that prenatal endomyocarditis might be responsible for congenital heart block. The mother of the Wood and Rogers [4] patient had had rheumatic infection in her pregnancy. There is no evidence that antenatal syphilis plays a rôle. One of the children with heart block was found at autopsy to have a lymphangio-endothelioma of the A–V node.[21]

The following two cases illustrate in general the points already outlined. The first one possesses interest from a diagnostic and prognostic standpoint in certain particulars not hitherto stressed.

Case I

A young man, aged 28, in vigorous health and of athletic type and habit, two hours after his usual horizontal bar exercise, September 19, 1930, developed a thumping in the heart region which had continued until he consulted me September 23. Shortly after the thumping began he developed a pain in the sternal region which continued during his waking hours until September 22; it was not agonizing but rather like a pressure. Neither the thumping nor the pain was aggravated by exercise and neither interfered with his sleep. When he awoke September 20 and 21 these symptoms reappeared. He continued with his work September 20, although whenever he got up he was dizzy. He still did not consider himself ill and drove his automobile for a week-end visit some forty miles on Saturday, September 20. On September 21, after he had retired he began to have cold sweats and waves of heat beginning at his legs and coming up over his body. He vomited after being given a purgative, and soon thereafter lost consciousness and apparently fell down trying to get out of bed. The noise of the fall brought his host into his room. The unconsciousness lasted five minutes. A doctor summoned found the pulse 24, and it remained 24–30 all day September 22. The patient drove himself back to town the morning of September 23, and at the time of his consultation (3 p.m.) felt as well as he ever did.

He had had measles, mumps, scarlet fever and pneumonia in childhood; denied having had rheumatism or diphtheria. He had had no venereal disease.

The physical examination revealed nothing of importance. The heart rate was 72 and regular. There was no murmur. The blood pressure was 108/70. The fluoroscopic examination revealed a heart of normal size. The next few days he continued to have dizzy spells. On September 26 he was examined for life insurance by another doctor who found the heart rate 40. By the time the patient came to me, half an hour later, the heart rate was again 72. An electrocardiogram was made immediately and fortunately he was caught in a period of complete block. This electrocardiogram, September 26, 1930, showed an inconstant atrioventricular block (2:1 at times, at other times no block was present); P.R., 0.28, when all auricular impulses passed to the ventricle; Q.R.S., 0.14 (intraventricular delay). R_1, R_2, R_3 slurred; left ventricular preponderance. He was given barium chloride ½ grain three times a day from September 28. On October 3 the note was made that he had had no

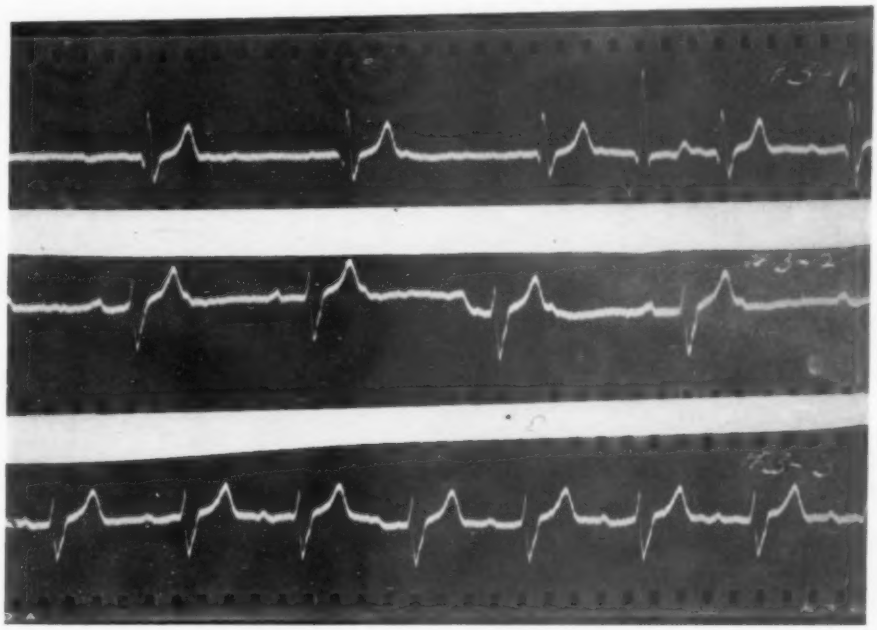


FIG. 1. Case I. (Age 28. 9/26/30.) Electrocardiogram: Inconstant atrioventricular block (2:1 at times, at other times no block was present). P.R., 0.28, when all auricular impulses passed to the ventricle. Q.R.S., 0.14 (intraventricular delay). R_1, R_2, R_3 slurred. Left ventricular preponderance.

dizzy spells. A second electrocardiogram was made October 4: Sinus rhythm; auricular and ventricular rate, 60; P.R., 0.16; Q.R.S., 0.12 (intraventricular delay); no atrioventricular block; R_1, R_3 notched; R_2 slurred; T_3 inverted; right ventricular preponderance. The barium was discontinued after October 23. In June 1931 he reported that he had had for three or four weeks fleeting sensations of imminent fainting three or four times daily. At times also he had had sharp sudden pains near the upper part of the sternum, only for a minute which cut short his breath. At this time the heart and pulse were 72. When seen on March 28, 1933, he reported that he had not had the slightest indication of trouble; no dizziness ever; had been swimming without discomfort; during this winter he had paddled a pirogue three or four miles, and had hunted, walking knee deep in water and mud, all without trouble. He had been married 18 months. The physical examination showed nothing new: heart, not

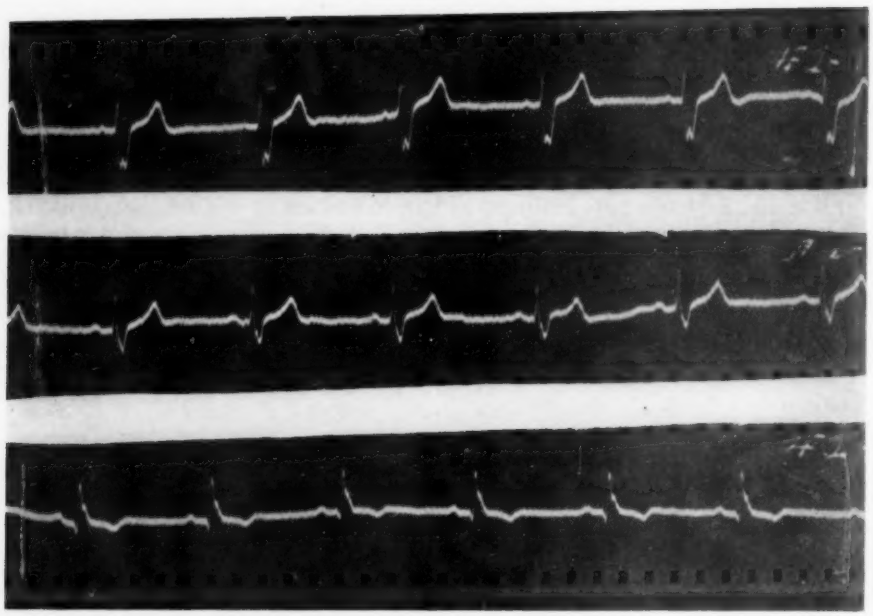


FIG. 2. Case I. (Age 28. 10/4/30.) Electrocardiogram: Sinus rhythm. Auricular and ventricular rate: 60. P.R., 0.16. Q.R.S., 0.12 (intraventricular delay). No atrioventricular block. R_1, R_3 notched; R_2 slurred; T_3 inverted. Right ventricular preponderance.

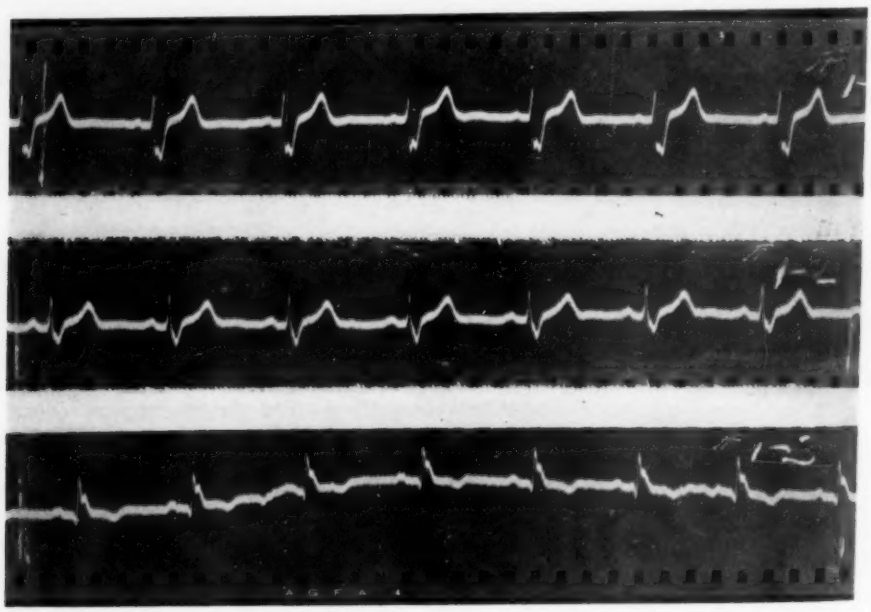


FIG. 3. Case I. (Age 28. 3/28/33.) Electrocardiogram: Auricular and ventricular rate: 65. P.R., 0.16. Q.R.S., 0.10. $S_{1\text{-}2\text{-}3}$ notched; T_3 inverted; $S\text{-}T_{1\text{-}2}$ elevated. Bundle branch block, probably right.

enlarged; no murmur. Blood pressure: 116/82. Electrocardiogram: auricular and ventricular rate 65; P.R., 0.16 +; Q.R.S., 0.10; S_{1-2-3} notched; T_3 inverted; $S\text{–}T_{1-2}$ elevated; bundle branch block, probably right.

Here then is a heart block of unknown etiology, apparently coming on abruptly, giving rise to frequent Stokes-Adams attacks which were controlled by the administration of barium chloride and did not return after its cessation. Although the electrocardiogram continued to show, after two and one-half years, evidence of intraventricular conduction disturbance (bundle branch block) the patient suffered no inconvenience. This patient differs from others reported: first in that the block was not constant; second that the Stokes-Adams symptoms were severe; and third that with the passing of the atrioventricular block there remained bundle branch block.

Case II

A young woman 23 years old was brought to my attention by Dr. W. R. Wirth. In 1928 she underwent a routine examination preparatory to entering gymnasium classes at the Y. W. C. A. Her slow pulse was noted and she was advised to consult her family doctor. When I saw her in December 1932, she had been attending these

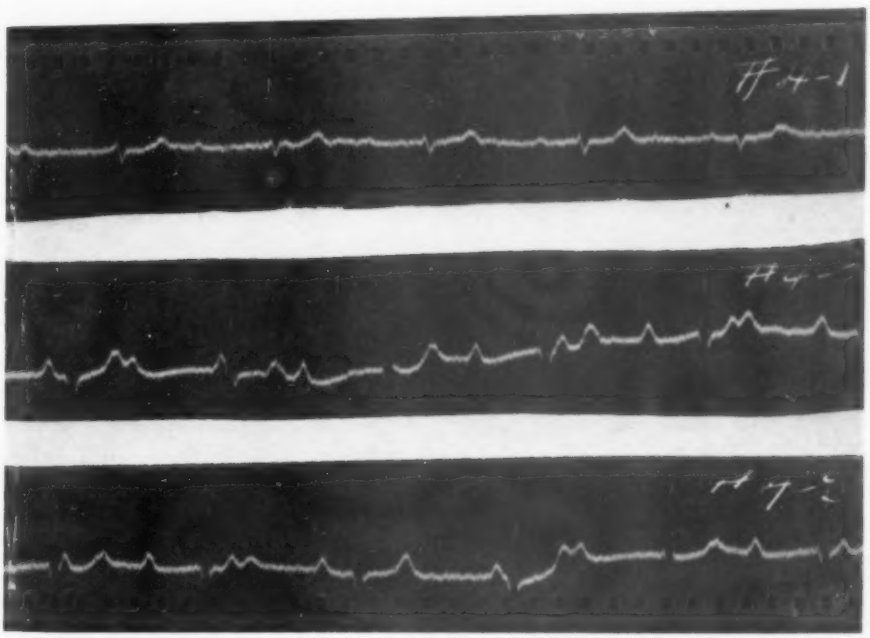


Fig. 4. Case II. (Age 23. 12/5/32.) Electrocardiogram: Complete atrioventricular block. Auricular rate: 90. Ventricular rate: 55. Q.R.S., 0.07. Right ventricular preponderance.

classes for four years. They consisted chiefly of setting up exercises. She felt no bad effects, rather she usually felt better after them. Swimming 40 feet, however, caused marked dyspnea; and she also had some dyspnea after dancing or after running three blocks. She had never fainted, nor had any dizziness. There was nothing of interest in her past history. She had had measles and mumps as a child; she denied having had diphtheria or rheumatism. Tonsillectomy had been performed in September 1930 on account of occasional sore throat. She had had influenza in 1918 but it was not severe.

The physical examination revealed a young woman in apparent full health, and was negative except for heart findings. Heart and pulse rate were 50, and regular. There was a loud systolic murmur at the apex transmitted out to the left anterior axillary line. The same murmur was heard over the base and over the whole precordium. Blood pressure 120/60. Fluoroscopic examination: no enlargement of the heart. On one occasion, when the patient was made to hop 100 times, the heart rate did not increase (56 before, 58 after hopping). Slight dyspnea was noted after exercise. Electrocardiogram: complete atrioventricular block; auricular rate 90; ventricular rate 55; Q.R.S., 0.07; right ventricular preponderance.

This patient with a heart block of unknown origin has suffered little or no inconvenience in the four years that it has been recognized or suspected. In the absence of any history of diphtheria or rheumatism, we must attribute it to the influenza in 1918, or to the frequent sore throat. The murmur represents, in all probability, the endocardial damage done by the same factor. We find no basis in the history, or in the physical examination, for assuming that the block is congenital, or due to septal anomaly.

Case III

This case was brought to my attention by Dr. Maurice Sullivan. A young man, aged 32, without complaint was sent home from one of the Civilian Reforestation Camps because of a bradycardia discovered at routine physical examination. Our physical examination showed the apex beat just beyond the left nipple line and a systolic murmur at the apex. The electrocardiogram revealed a complete atrioventricular block, the auricular rate being 65, the ventricular 42. The patient denied ever having been ill except for influenza in 1918.

Case IV

A young woman aged 31, in apparently perfect health, had two attacks of syncope in which the heart rate was counted by competent physicians as 30. An electrocardiogram taken in an interval failed, however, to show any disturbance of rhythm or conduction. We can, therefore, only surmise that we were dealing with a transitory block.

Summary

A review of the literature shows that heart block in the young is by no means a rare condition. Of approximately 100 cases, about 42 per cent are congenital and associated with a developmental deformity. Diphtheria, rheumatism and influenza are important etiological factors. There is reason to believe that heart block in hearts not the site of degenerative changes is not incompatible with long life. Many patients have no Stokes-Adams attacks and suffer no inconvenience. On the other hand, the possibility of its existence should be considered when we are dealing with fainting spells and convulsive movements in the young.

REFERENCES

1. White, P.: Heart disease, 1931, Macmillan Company, New York, p. 673.
2. Archigène, D.: Thèse de Paris, 1927.
3. Yater, W. M.: Congenital heart block; review of literature; report of case with incomplete heterotaxy; electrocardiogram in dextrocardia, Am. Jr. Dis. Child., 1929, xxxviii, 112–136.

4. Wood, W. A., and Rogers, H.: Congenital heart block; report of case, Calif. and West. Med., 1932, xxxvi, 397–398.
5. Sprague, H. B., and White, P. D.: High-grade heart block under age of thirty, Med. Clin. North Am., 1927, x, 1235–1250.
6. de Massary and Lian: Quoted by Archigène.[2]
7. Jeannin, C., and Clerc, A.: Dissociation auriculo-ventriculaire et grossesse, Bull. et mém. Soc. méd. d. hôp. de Paris, 1927, li, 122–127.
Clerc, A., and Levy, R.: Evolution de la dissociation auriculo-ventriculaire chez les jeunes sujets, Bull. et mém. Soc. méd. d. hôp. de Paris, 1928, lii, 490–498.
Laubry: Quoted by Archigène.[2]
Titus, R. S., and Stevens, W. B.: Normal pregnancy in patient with preëxisting complete heart block, Am. Jr. Obst. and Gynec., 1931, xxii, 773–777.
Dressler, W.: Schwangerschaft und Herzblock, Wien. Arch. f. inn. Med., 1927, xiv, 83–96.
Herrmann, G., and King, E. L.: Cardiovascular disturbances in the obstetric patient, Jr. Am. Med. Assoc., 1930, xcv, 1472–1476.
8. Clerc, A., and Levy, R.: Evolution de la dissociation auriculo-ventriculaire chez les jeunes sujets, Bull. et mém. Soc. méd. d. hôp. de Paris, 1928, lii, 490–498.
9. Calandre: Quoted by Archigène.[2]
10. Zander: Quoted by Clerc and Levy.[8]
11. Taussig: Quoted by Archigène.[2]
12. Jacquier: Quoted by Archigène.[2]
13. Willius, F. A.: Complete heart block of unusually long duration, Proc. Staff Meet., Mayo Clinic, 1931, vi, 196–200.
14. Hyman, H. T.: Asymptomatic heart block of long duration, Jr. Am. Med. Assoc., 1930, xciv, 27.
15. Aldrich: Quoted by Lampard, M. E.: Heart block associated with congenital heart disease, Arch. Dis. Childhood, 1928, iii, 212–220.
16. Butler, S., and Levine, S. A.: Diphtheria as cause of late heart block, Am. Heart Jr., 1930, v, 592–598.
17. Švejcar and Francová-Helbichova, A.: Rare case of congenital cardiopathy associated with sino-auricular block in infant, Časop. lék. česk., 1931, lxx, 1775–1777.
18. Godfrey, J. W., and Palmer, R. S.: Congenital complete heart block; report of additional case, New Eng. Jr. Med., 1932, ccvii, 575–577.
19. Carter, E. P., and Howland, J.: Occurrence of congenital atrio-ventricular dissociation; report of case of congenital complete heart block, Bull. Johns Hopkins Hosp., 1920, xxxi, 351.
20. Wilson, J. G., and Grant, R. T.: A case of congenital malformation of the heart in an infant associated with partial heart block, Heart, 1925, xii, 295–305.
Yater, W. M.: Congenital heart block, report of case with incomplete heterotaxy, Proc. Staff Meet., Mayo Clinic, 1928, iii, 320–322.
Abbott: Personal communication to White. Quoted by Godfrey and Palmer.[18]
Perotti: Quoted by Yater.[3]
21. Armstrong, H., and Mönckeberg, J. G.: Herzblock, bedingt durch primären Herztumor, bei einem 5-jährigen Kind, Deutsch. Arch. f. klin. Med., 1911, cii, 144–166.

EDITORIAL

AMEBIASIS

THE REPORTS in the press of an outbreak of amebic dysentery in Chicago, which has apparently been traced to infected food handlers, should draw the attention of the medical profession to what Craig [1] has called " the amebiasis problem."

Though amebic dysentery and its most frequent complication, hepatic abscess, are seen with relative frequency in the southern states and are not rare in the northern part of this country, it is not in connection with these outspoken clinical manifestations of amebiasis that the main problem exists; it is rather with the far greater number of instances in which amebiasis is present without producing any characteristic symptoms. The stools of these latent cases of amebiasis are more apt to contain the *Endameba histolytica* in its encysted than in its vegetative form, and since it is the amebic cyst which serves to transmit the disease, each latent case is a potential source of danger to others. The disease which is latent in the " carrier " may, when transmitted to another, assume a virulent dysenteric form. Human " carriers " are believed to constitute the chief source from which, by transmission of infected fecal material, arise the acute cases of amebic dysentery in this country. The rôle of certain animals, rats, pigs and dogs, which have been shown to be occasional carriers, is probably a relatively minor one. The amebic cysts in human or animal feces are sufficiently resistant to remain viable for a number of days, or even weeks in a moist medium.[2] Flies may carry such infected fecal material in their digestive canals and deposit amebic cysts in their feces on human food. Water supplies may become infected and serve as a medium for the transmission of the cysts. More usually it is the hands of the " carrier " which become contaminated and inoculate the food supply of others. The carrier who is also a food handler is the chief source of danger. A survey in Chicago in 1927 showed that 2.35 per cent of the 1148 food handlers examined were carriers of the *Endameba histolytica*.[3]

An even more important aspect of the problem of latent amebiasis is the possible effect of the chronic subclinical infection on the carrier himself. The number of cases of amebic dysentery and of amebic abscess that occur in this country yearly cannot be exactly stated, but to judge by the reported cases this number would not exceed a few thousand. The results of surveys by competent authorities would indicate, however, that the cases of latent amebiasis in the United States must be numbered in the millions.

[1] CRAIG, C. F.: The amebiasis problem, Jr. Am. Med. Assoc., 1932, xcviii, 1615–1620.

[2] WIGHT, T., and WIGHT, V.: On the viability of cysts of *Endameba histolytica* under variable conditions, Am. Jr. Trop. Med., 1932, xii, 381–387.

[3] WILLIAMSON, C. S., KAPLAN, B., and GEIGER, J. C.: A survey of amebic dysentery in Chicago, Jr. Am. Med. Assoc., 1929, xcii, 528.

Craig,[1] in 1932, after a review of these surveys, concluded that "enough has been done to warrant the statement that it is conservative to estimate that between 5 and 10 per cent of the people of this country harbor *Endameba histolytica.*"

The results of these surveys have been discounted by some on the assumption that there must exist avirulent strains of endameba not readily distinguishable from the *Endameba histolytica.* Brumpt has described such avirulent species. His work, however, lacks confirmation and is contradicted by the mass of experimental work showing that the cysts from cases of asymptomatic amebiasis are pathogenic to animals and, as Walker and Sellards showed, also to man. A more difficult question to answer is whether latent amebiasis in humans is always accompanied by pathological lesions. Evidence to the contrary is not available, but neither is there on record a sufficient number of autopsy studies on cases of latent amebiasis to yield conviction that lesions in the intestines of such cases are always present. The most important contribution in this field is that of Bartlett,[4] from Egypt, during the World War. He described the postmortem findings in 11 cases which had never in life presented symptoms of diarrhea or dysentery but had shown *Endameba histolytica* in their stools. All were found to show amebic ulcerations, in some instances extensive, in their colons. Sufficient scattered similar cases are on record to show conclusively that very definite lesions may exist without sufficient symptoms to attract attention. It is believed by some that a constant process of formation and healing of small ulcers probably goes on in the large bowel of these asymptomatic cases. On the other hand, Andrews and Atchley[5] found little evidence of occult blood in the feces of carriers of *Endameba histolytica.* From animal experiments it would seem that the endameba cannot persist in the lumen of the bowel without attacking the mucosa. In view of the importance of the question, it is highly desirable that further investigations should be carried out.

A conservative position must likewise be taken as to the question of constitutional symptoms due to latent amebiasis. It is certain that many cases are entirely asymptomatic. It is probable, however, that in certain instances vague digestive discomforts, neuralgias and general asthenia, may be caused by the otherwise latent amebic infection.

In view of the constant advances that have been made in the therapy of amebiasis, it is perhaps reasonable to believe that a safe, efficient, and not too expensive remedy may be available with which to attack the problem offered by the truly appalling number of latent cases of this disease.

It is apparent, however, that no program can, nor perhaps should be formulated, until further data have been accumulated bearing on the pathology and the constitutional effects in humans of latent amebiasis. The collection of such data is almost entirely dependent upon an awakening of

[4] Bartlett, C.: Quart. Jr. Med., 1917, x, 185; Quoted by Craig, C. F.: Pathology of amebiasis in carriers, Am. Jr. Trop. Med., 1932, xii, 285–299.

[5] Andrews, J., and Atchley, F.: Negative occult blood tests in carriers of dysentery-producing *Endameba histolytica,* Jr. Am. Med. Assoc., 1932, xcix, 1340–1342.

interest among physicians as to the practical importance of this whole question. So far, we owe our knowledge of the subject largely to the devoted labors of a relatively few men many of whom are primarily parasitologists. The clinician has the opportunity to make important further contributions.

The average hospital has lagged far behind present day methods in the diagnosis of amebiasis. Parasitology is in general the weakest department in most clinical laboratories. The examination of the stool is usually the most perfunctorily carried out of all laboratory procedures. Dougherty [6] reports results obtained from the records of the larger hospitals in 13 southern cities between 1927 and 1931: "*Endameba histolytica* was demonstrated in the stools of 396 cases reported, and out of this number 336 were in hospitals with complaints directly referable to acute or chronic amebic dysentery or abscess of the liver." One must deduce that in five years in the larger hospitals of 13 cities only 60 cases of latent amebiasis were discovered. During this same period in 1930 Faust [7] conducted a survey of the patients in the Charité Hospital in New Orleans. He found 27.2 per cent of infections with the endameba in the male medical wards, 13.1 per cent in patients in the female medical wards, 25.2 per cent in the obstetrical wards and 8.27 per cent in medical students. His single survey of only 1100 individuals disclosed 150 cases of amebiasis. The failure of our present routine diagnostic measures in general hospitals can scarcely be more strikingly demonstrated. It is probable that the more general adoption of cultural methods for the ameba would result in an awakening of fresh interest in the diagnosis of amebiasis. The preparation of the medium has of late been much simplified. The growth contains the protozoa in the vegetative form and in relative abundance, especially in subculture. The time involved is probably no greater than what is required for adequate examination of fresh specimens and less than that demanded by the preparation and study of hematoxylin stained smears. Moreover the cultural method in many hands (Stitt,[8] Craig, Spector [9]) yields a higher percentage of positives than study of smears. Finally, the stimulus of definite diagnostic findings might awaken physicians and clinical pathologists to a more careful consideration of the clinical aspects of these latent forms of amebic infection.

[6] Daugherty, M. S., Jr.: Amebiasis, a public health problem in the cities of the southern United States, Am. Jr. Trop. Med., 1933, xiii, 317–327.

[7] Faust, E. C.: The incidence and significance of infestation with *Endameba histolytica* in New Orleans and the American tropics, Am. Jr. Trop. Med., 1931, xi, 231.

[8] Stitt, E. R.: The diagnostics and treatment of tropical diseases, 5th Edition, 1929, P. Blakiston Sons and Co., Philadelphia, p. 193.

[9] Spector, B. K.: A comparative study of cultural and immunological methods of diagnosing infections with *Endameba histolytica*, Jr. Prev. Med., 1932, vi, 117–128.

REVIEWS

Life in the Making. By ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University; with the assistance of ELLERY RAND. 297 pages. The Viking Press, New York. 1933. Price, $2.75.

The author, in a free-flowing and interesting style, has recorded the story of the development of our present knowledge of sex. He has brought into a logical sequence facts that to most of us were uncorrelated bits of sex knowledge. In so doing he has drawn upon a wide knowledge of very diverse realms of scientific literature, and has given to his book real value as a reference volume.

The book is divided into six parts. The first deals with the numerous misconceptions that have arisen during the ages concerning the way in which life begins and ends, with a detailed account of our present knowledge of the sperm and egg. The second part deals with different types of sex behavior. Here the author does not limit himself to man but records many of the observations that have been made of the sex life of animals. This portion of the book will be of as much interest to the biologist as to the physician. Indeed, the reviewer, who happens to be a physician, believes he found this section interested him more than did any other part of the whole book. Another section points out that in spite of the numerous advances that have been made in sex knowledge, man is today still as unable to control sex or even to determine sex before birth as he ever was. The last section of this book deals with twins, and because the author himself is an identical twin the records of his personal feelings on this matter have a special appeal.

Nurses, physicians, and biologists will find this book of great interest, but possibly the average adult layman, for whom the book has been especially written, will be disappointed. The rather startling outer cover will be likely to attract the layman, but the very complete historical sketches, combined with the great number of scientific facts, may overwhelm him and cause him to lose interest. These same features are the elements that make Dr. Guttmacher's work of great value to all those really interested in biological and medical problems, and of particular interest to those who specialize in obstetrics and gynecology.

L. B.

Osteitis Deformans. A Review of the Literature and Report of Eleven Cases. Public Health Service Bulletin No. 209. By J. W. KERR, Medical Director, United States Public Health Service. Washington: Government Printing Office. 1933. Price, 10 cents.

This Bulletin, comprising 122 pages with bibliography, contains a review of reports appearing in the literature during the period 1876 to 1928 and also reports upon 11 additional cases from among beneficiaries of the Public Health Service. The analysis is approached from the standpoint of the history of the disease, its geographical distribution, and the occurrence of similar disease in animals. Its frequency in man, hereditary factors, race, sex, color, occupation, mental status, environment, habits, and mental attitude of patients are considered. General symptomatology, order of involvement of bones, other features such as the appearance of syphilis and malignancy, and associated disorders of the vascular and genito-urinary system, blood, skin and its appendages, eye, ear, neurological and psychiatric components are discussed. The chemistry, changes in ductless glands, and other pathological bone changes are referred to. Salient points in diagnosis are outlined and past views on treatment recorded.

The outstanding features of the disease as reported appear to be a greater prevalence in cold climates, hereditary factors, lack of association with syphilis, its liability to affect the special senses, and sarcomatous formation. From a pathological standpoint, the author considers the disease closely related to osteomalacia and possibly identical with osteitis fibrosa and leontiasis ossea. Because of their similarity in pathology during some stage of the disease, the author suspects that all may be due to the same underlying cause. He says: "Its etiology is unknown. Discovery of the cause will probably throw light on this whole group of diseases. Every effort should be made to detect cases and record the results. Systematic research should be conducted to clarify the etiology and abnormal metabolism. The bearing of heredity, the functions of the internal secretions, the newer views regarding nutrition and the tendency to malignancy should all be taken into account in attempts to throw light on the underlying cause of the affection."

W. L. T.

Psychoanalysis and Medicine. A Study of the Wish to Fall Ill. By KARIN STEPHEN, M.A., M.R.C.S., L.R.C.P.; Sometime Fellow of Newnham College, Cambridge. 238 pages. The MacMillan Company, New York. 1933. Price, $2.50.

Dr. Ernest Jones, in a short preface to this book, states: "It would be hard to think of a better introduction to this complex study, than that which her book offers." With this statement, we heartily agree. Written in a clear, logical manner, it is free from the exaggerations that so frequently mar books on the subject of psychoanalysis. The average physician may not agree with many of the concepts here elucidated, but he will nevertheless find much that is helpful in understanding the chronic invalid. Although of chief value as an aid in dealing with psychoneurotic conditions, it should be of help in understanding the mental phases of organic disease.

A. C. G.

History of Urology. Volumes I and II. Editorial Committee: BRANSFORD LEWIS, Chairman; EDGAR G. BALLENGER; WILLIAM A. FRONTZ; and HOMER G. HAMER. xi + 385; 17 x 24 cm. Williams and Wilkins, Baltimore. 1933. Price, $8.00 for 2 volumes.

This two-volume work on the history of urology was prepared under the auspices of the American Urological Association, and has been written by the editorial committee composed of Drs. Bransford Lewis, Edgar G. Ballenger, Homer G. Hamer, and William A. Frontz, together with 26 other collaborators.

While it is a general history of urology and depicts in a very interesting way the knowledge of this specialty back to early historic times, the greater bulk of the work is, nevertheless, devoted to a more detailed exposition of the history of urology in the United States. Special sections are given over to the description of the development of urology in certain selected American medical centers. In addition to this geographic method of presenting material, there are separate chapters on special topics, such as, "Tests and Chemicals," "Diagnosis in Urology," "Focal Infections," and "Bacteriology." For the most part the book is very readable, even for those whose main interests are not in this field; it is always interesting, and in some sections it is distinctly amusing.

The striking advances made in this specialty and the great reduction in operative mortality in the surgical procedures are forcibly presented. These volumes constitute a noteworthy contribution to the history of modern medicine. They will interest not only urologists, but all physicians who wish to obtain a sound perspective in considering the value of specialization, or who desire to acquaint themselves with the status of modern urology.

M. C. P.

To Be or Not to Be. A Study of Suicide. By LOUIS I. DUBLIN, Ph.D., and BESSIE BUNZEL, M.A. Harrison Smith and Robert Haas, New York. 1933.

The statistical method has been the chief tool at the disposal of the authors for a study of suicide. They have brought together the main facts on the subject, pointing out, however, that there are many aspects of the problem and that it is not possible to cover all of them in a small volume. They have compiled data on the frequency of suicide among various groups; on the changing rates from year to year; on the age, sex, and racial factors; on urban and rural incidence; together with methods used by those taking their own lives. Factual material derived from older historical, philosophical and religious sources are presented, with a compilation of the scattered findings of other investigators.

The book touches upon suicide among primitive people; upon the teachings, religious and ethical, which tend to encourage or prohibit; upon the prevailing sentiments and customs being crystallized in law; and upon causes and prevention. Hardships of various kinds, including ill health, mental abnormality, physical pain, deformity, loss of honor, position, freedom, and love are all mentioned as objective causes. But aside from this, the authors point out that there is the more important factor of the serious emotional maladjustments and conflicts that underlie attempts at suicide. These individual emotional conflicts which often lead to suicide are in other instances modified, sublimated, or given a conventional solution in accordance with public opinion.

The authors regard prevention of suicide as involving an understanding and an appreciation of the individual motives and emotional conflicts lying behind such attempts. They review some of the mental mechanisms prompting such acts and describe plans already in operation for the prevention of suicide.

W. L. T.

The Adolescent Boy. By WINIFRED V. RICHMOND, Ph.D., Psychologist, George Washington University, and St. Elizabeth's Hospital, Washington, D. C. 233 pages. Farrar and Rinehart, New York. 1933. Price, $2.50.

Adolescence: Studies in Mental Hygiene. By FRANKWOOD E. WILLIAMS, M.D., former Medical Director, National Committee for Mental Hygiene. 279 pages. Farrar and Rinehart. 1930. Price, $2.50.

Physicians are frequently faced with the necessity of counselling parents and their adolescent patients during the "crisis of life." Not all physicians have had the good fortune in their medical school days to have a series of lectures on the psychology of childhood, nor have they been able to complete a course of instruction in a child guidance clinic. These two books which, since they deal with different aspects of this subject, are here reviewed together, constitute an excellent symposium on the problems of adolescent adjustment.

Dr. Williams' book, which has gone through three large printings, is a collection of eleven of his previously published essays. It is a volume which will appeal to the sophisticated reader, inciting critical thought and challenging clearer thinking. On the other hand, it will give very little solace to the troubled parent.

The book is readable and lends itself well to quotation. Something of its quality and the author's point of view may be gained from some excerpts. "Mental Hygiene, like medicine, is an art not a science. . . . Ability to work in the field of mental hygiene is not a matter of good will or good intentions. It is a matter of knowledge. It is a field for the expertly trained. . . . At present the field is one for coöperative effort on the part of the psychiatrists, psychologists, educators and social workers, and success comes from a pooling of effort." "We try to force upon youngsters very unhealthy ideals. . . . Nobody knows as does the psychiatrist how devastating the damage has been to thousands of men and women through . . . these unhealthy ideas." "Parenthood is the only profession that can be practiced in America without definite instruction and preparation. Any one may become a parent. One learns, therefore,

on the job while occupied at the same time with many other time-consuming and energy-consuming jobs. There is no more inadequate method of learning than this nor one more wasteful of material. It is not surprising, therefore, that out of this situation come emotionally warped and misshapen personalities, some who protest vigorously—through their delinquency—others who become overpowered and tend to give up the conflict or to minimize it by retiring emotionally within themselves, a more agreeable type of child but probably a less healthy type than the former."

Dr. Richmond first wrote a book on the "Adolescent Girl," and apparently its success has led to the production of this very easily read and logically constructed book of eight chapters on the "opposite sex." It begins with a survey of the anthropological and historical background against which our modern youth must play his part, then logically takes up the problems of puberty with its deficiencies and abnormalities. As crime in recent years has become a very definite problem of adolescence, there is a discussion of the delinquent boy; but fortunately more than half of the balance of the book is devoted to the normal adolescent. It concludes with a discussion of "The Boy at College" and "The Young Man and the Changing World." The author reminds us that "in the light of our present knowledge we can review the mistakes of their up-bringing, can wish that we had been less arrogant, less short-sighted, less occupied with material things, and more interested in the intangible values of life. We have not given them the full measure of our confidence and understanding and even what we might have given them in preparation for the hardships they must undertake."

J. L. McC.

Mental Deficiency Due to Birth Injuries. By EDGAR H. DOLL, Ph.D., WINTHROP M. PHELPS, M.D., and RUTH T. MELCHER, M.A., Training School at Vineland, N. J. 275 pages. Macmillan Company, New York. 1932. Price, $4.50.

This book represents a very thorough study of birth injuries in the leading institution of this country for the care of mentally defective individuals. It is a timely report because of the ever apparent results of poorly handled obstetrical cases. As is pointed out in the preface: "The limitations of professional information and skill . . . render both diagnosis and treatment experimental, no matter from what angle the patient was considered. The best medical judgments describe the condition as Little's Disease, and offered no hope of amelioration."

This book thoroughly reviews the literature on the subject of birth accidents and analyzes the diagnosis of these neurologically handicapped patients. The book is fully illustrated and takes up the case histories of twelve such cases. A full bibliography, also, is given.

There is a great deal of misunderstanding in the medical profession on the matter of mental ability as measured through its functional expressions, language or movement. Unfortunately, the average practitioner does not realize that standards of normal mental development are built upon observation of total responses of mentally and physically average children in given situations. When a person is so seriously limited in motor activity as to interfere with his ability to express himself either through language or manipulation or both, we cannot directly compare his responses to test situations with those of the average child. Fortunately, this book fully discusses this question and helps to evaluate mental testing of neurologically injured persons.

Perhaps the most interesting and most valuable part of the book is the chapter on Physical Therapy which takes up the training of these unfortunates and gives a ray of hope to the obstetrician who has officiated at bringing into the world a child who apparently is doomed to a life of hopelessness.

The reviewer feels that this book is well worth the time it takes to read it, and that it will stimulate further research in this very important subject.

J. L. McC.

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts of publications to the Library by members of the College:

Dr. Milton A. Bridges (Fellow), New York, N. Y.—one book, "Dietetics for the Clinician";
Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J.—one reprint;
Dr. Oscar W. Bethea (Fellow), New Orleans, La.—five reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint;
Dr. Ronald L. Hamilton (Fellow), Sayre, Pa.—two reprints;
Dr. George H. Hoxie (Fellow), Kansas City, Mo.—two reprints;
Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—two reprints;
Dr. Frederick R. Taylor (Fellow), High Point, N. C.—one reprint;
Dr. John Russell Twiss (Fellow), New York, N. Y.—three reprints;
Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—one reprint.

Dr. William R. Brooksher (Fellow), Fort Smith, Ark., was elected Secretary-Treasurer of the Arkansas Medical Society at a meeting of its Council in Little Rock, September 15.

Under the Presidency of Dr. Joseph Yampolsky (Fellow), Atlanta, Ga., the first annual scientific meeting of the Georgia Pediatric Society was held in Atlanta, October 12.

Dr. Horton Casparis (Fellow), Nashville, Tenn., was one of the guest speakers, his subject being "Allergy in Children."

Dr. Janvier W. Lindsay (Fellow), Washington, D. C., has been named to serve for a term of three years as Chairman of a Committee appointed by the President of the Medical Society of the District of Columbia to supervise a tumor registry established recently by the Society.

Dr. Walter J. Freeman (Fellow) and Dr. Matthew White Perry (Fellow), both of Washington, D. C., were also appointed members of the Committee to serve for terms of three years each.

Dr. Waller S. Leathers (Fellow), Nashville, Tenn., was elected Chairman of the newly created Public Health Council at its first meeting in Nashville during September.

Dr. Albert F. Tyler (Fellow), Omaha, Nebr., was installed as President of the American Congress on Physical Therapy at its last annual meeting.

Dr. John S. Hibben (Associate), Pasadena, Calif., was elected one of the Vice-Presidents.

The Radiological Society of North America, the American Roentgen-Ray Society, the American Radium Society and the American College of Radiology com-

bined their meetings under the title of the American Congress on Radiology at Chicago, September 25–30.

Dr. John T. Murphy (Fellow), Toledo, Ohio, and Dr. George W. Grier (Fellow), Pittsburgh, Pa., were elected President and President-Elect, respectively, of the American Roentgen-Ray Society.

Dr. Rollin H. Stevens (Fellow), Detroit, was elected President of the American Radium Society.

Dr. Thomas A. Groover (Fellow), Washington, D. C., and Dr. Benjamin H. Orndoff (Fellow), Chicago, were elected President-Elect and Secretary, respectively, of the American College of Radiology.

Dr. Harlow Brooks (Fellow), New York City, and Dr. Elliott P. Joslin (Fellow), Boston, were guest speakers at the fourth annual fall Clinical Conference sponsored by the Oklahoma Clinical Society, October 30 to November 2.

The following changes were made in a recent reorganization of the clinical departments of the College of Medical Evangelists, Los Angeles. Those reported refer only to members of the College.

Dr. Charles C. Browning (Fellow), Emeritus Professor of Tuberculosis;
Dr. John V. Barrow (Fellow), Director of Clinical Teaching in the Department of Medicine, Los Angeles County General Hospital;
Dr. Carl R. Howson (Fellow), promoted to Professor and Head of the Department of Tuberculosis;
Dr. Ben E. Grant, Jr. (Fellow), Associate Professor of Medicine.

Dr. Allen K. Krause (Fellow), Tucson, Ariz., Dr. Leonard G. Rowntree (Fellow), Philadelphia, Pa., and Dr. John H. Musser (Fellow), New Orleans, La., were among the guest speakers delivering lectures at the second Post Graduate Medical Assembly of South Texas at Houston, November 21 to 24.

Dr. Louis Faugeres Bishop, Jr. (Fellow), of New York, was appointed to the faculty of postgraduate medical study, University of Oklahoma, School of Medicine, for a circuit course, October 9 to 13, Management of Coronary Artery Disease.

A Central Malaria Library

A malaria library was founded in Rome by the Stazione Sperimentale per la Lotta Antimalarica in 1925, and an "Index to Malaria Literature" is issued annually by the Station.

To make this as complete a central malaria library as possible, the Director of the Library appeals to all malariologists to send books and reprints of articles on malaria. Photostat copies of any articles in the library can be had on request, at cost of production.

All publications and requests should be addressed to: The Director, Stazione Sperimentale per la Lotta Antimalarica, Corso Vittorio Emanuele 168, Rome (16).

OBITUARIES

DR. SAMUEL FRANKLIN ADAMS

Samuel Franklin Adams, M.D., M.S. in Medicine (University of Minnesota), F.A.C.P., died suddenly, September 28, while traveling by ambulance from his home in White Plains, New York, to the Grasslands Hospital, Valhalla, New York. He was suffering from pneumonia of only twenty-four hours' duration, and it was not suspected that any condition existed which might prove fatal.

Dr. Adams was born in Jersey City, New Jersey, July 27, 1896. He attended Dickinson High School, Jersey City, the University of Pennsylvania 1914–1915, and Wesleyan University, Middletown, Connecticut, 1915–1916. In 1916 he entered New York Homeopathic Hospital and Flower Hospital from which he was graduated in 1920. After a year's internship in Buffalo Homeopathic Hospital and three months of practice in Jersey City, he entered The Mayo Foundation September 28, 1921, as a fellow in medicine. In 1922, he was appointed first assistant in a section on medicine of The Mayo Clinic, associate in 1925, and in 1927 instructor in medicine, The Mayo Foundation, Graduate School, University of Minnesota. He was made a Fellow of the American College of Physicians in 1926.

In 1931, Dr. Adams left The Mayo Clinic to enter practice in New York City. At the time of his death he was assistant professor of medicine at his alma mater; on the staffs of the Flower Hospital and the Metropolitan Hospital, New York, and of St. Agnes' Hospital, White Plains, and White Plains Hospital. He was also on the staff of Grasslands Hospital, Valhalla, New York, where he had organized a metabolic clinic of which he was the head. He was a Fellow of the American Medical Association, a member of Sigma Xi, and a member of the Central Society for Clinical Research.

A record such as this needs little amplification, but there are matters, fully as important, concerning which a bare list of achievements is silent. Dr. Adams' too short medical career almost corresponded with the first ten years of insulin treatment of diabetes, and of the twenty some medical papers which bear his name, three-fourths are on the subject of diabetes. His field of second interest was disease of the blood vessels, in which, as in other branches of medicine, he was recognized as a brilliant student and internist.

With all of his ability in his work, Dr. Adams was nothing of the grind. Apparently, mastery of difficult subjects came to him without effort. And so it was with his avocations. His wit, energy and broad reading, and his ability in music and in sports made him the center of any gathering in which he found himself. At various times and in various social or semi-professional organizations Dr. Adams was elected to the presidency or to

some other office of responsibility, the duties of which he discharged with universal satisfaction.

In 1920, Dr. Adams married Miss Ethel S. Greene who, with three children, survives him.

GEORGE E. BROWN, M.D., F.A.C.P.,
Rochester, Minn.

DR. WILLIAM RAY BATHURST

Death removed one of the outstanding members of the Arkansas medical profession when Dr. William Ray Bathurst died suddenly August 31, 1933, at the age of 57.

A native of Pennsylvania, most of his professional career was spent in Arkansas where he had served well both his patients and his associates. Following his graduation from the Medical Department of the University of South in 1899, Dr. Bathurst studied at the Philadelphia Polyclinic Hospital, the New York Polyclinic Hospital and in Europe. His specialty was dermatology and syphilology, and since 1907 he was Professor of Dermatology in the Medical Department of the University of Arkansas.

One of his primary activities at the time of his death was the secretaryship of the Arkansas Medical Society and the editorship of the society's journal, offices which he had occupied since 1919. Always working for the best interests of his community, it was largely through his influence that the Arkansas basic science law became a reality. He was one of the originators of the Section of Dermatology of the Southern Medical Association. In 1928, Dr. Bathurst was elected President of the Southern Medical Association. He served his County Medical Society as treasurer for several years. He was a member of the House of Delegates of the American Medical Association 1920–1928, 1930, 1932, and 1933. In 1924, he was elected to Fellowship in the American College of Physicians.

Although he had been aware of some cardiac involvement for about two years, Dr. Bathurst did little to curtail his work. Thinking that he suffered only a passing indisposition, he absented himself from his office a day. During the night, the angel of death spread her wings.

An able dermatologist, an indefatigable worker, a progressive citizen, a gracious host, a gentleman always, William Ray Bathurst will long be revered in Arkansas medical annals.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas.